# Scientific Evidence Proving Vaccines

# Cause

# Type I, Insulin Dependent Diabetes (IDDM)

**John Barthelow Classen, MD**

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**Outline**

# I. Introduction: Proof Vaccines Cause IDDM

Vaccines have been linked to the development of certain autoimmune diseases in the past. The data included in this text proves vaccines cause Type I, insulin dependent diabetes mellitus (IDDM), an autoimmune disease. The cumulative risk of vaccine induced IDDM in people receiving standard immunization schedules is quantified **(Section VII)** using epidemiology studies and the risk is very large, relative risk > 3.5. This indicates the majority of cases of IDDM, in people who have received many standard immunizations, are vaccine induced. In US navy where employees are heavily immunized the risk of IDDM approaches 5.5 times that in civilians **(Section VI, 10).**

The Merriam-Webster dictionary (1974) defines the word **prove** using the following definitions: "To test by experiment or by a **standard**; to establish the truth of by argument or evidence; to show to be correct, valid, or genuine." Unanimous acceptance is not necessary for proving toxicology nor is 100% consistency of the data. Dissenters exists to challenge all facts and widely held beliefs. Many times the dissenters persist because the facts are contrary to their financial interests or challenge their own work and hence affect their careers. This is common when commercial products are proven to be toxic. The dissenters base their beliefs on data from flawed studies, and statistical anomalies. The later is the case with people who challenge the existence of vaccine induced IDDM as discussed below **(Section VIII).**

To prove an drug or vaccine causes an improvement in a health outcome the **standard** often requires a clinical trial to be performed. The size of these clinical trials has often been established and written into the law. For example in the US a live rubella vaccine must be tested in 10,000 individuals ( CFR 21:630.60 d). Generally a group of patients receive the intervention in question and a second group receives no treatment or an alternate treatment. The desired outcome for proof is a statistically significant improvement in a health outcome, $p=0.05$. Even in the later case a statistical value of $p=0.05$ indicates there is a 5% chance that random variation caused the effect seen, and the intervention has no beneficial effect on the health outcome. In some cases, studies to prove efficacy involve testing to see if the new drug gives an result comparable to a different drug, usually an older product already on the market. The study designs involves testing to see if the older drug has a statistically significant better outcome than the test drug. In general only a single trial is necessary to prove efficacy but two are required for some drugs. Animal models of diseases and a well defined mechanism of action are not necessary. This is consistent with FDA guidelines for approval of drugs (CFR 21) .

The **standard** for proving a causal relationship in the field of toxicology is different than the standard to prove a causal improvement of health. It is unethical to perform clinical trials to prove that an agent is deleterious to one's health. It is also generally impossible to perform such a study since patients are not willingly volunteer to join a study and have their health destroyed. Use of captive populations such as using criminals and prisoner of wars to prove such a theory is unethical and not permitted. A clinical trial has never been performed to show smokers are at

increased risk of lung disease because it would be unethical to try to convince people in a treatment group to start smoking. In the same way it would be unethical to intentionally expose subjects to radiation or asbestos to determine if the subjects are at increased risk for disease. Instead a causal relationship between commercial products and adverse events is proven by one or more of the following: the presence of one or more plausible mechanisms of action, in vitro laboratory studies, animal toxicity data, and epidemiology data. This standard has been applied to prove tobacco, asbestos, and radiation are unhealthy to humans. The data, discussed below, which links vaccines and IDDM meets the standard for proving a causal association as defined above.

Biological plausibility **(Section III)** provides proof that vaccines can cause insulin dependent diabetes. For example it has been clearly shown that alpha interferon causes IDDM. Many vaccines stimulate macrophages which release alpha interferon. It is thus a certainty that immunization of billions of people with many doses of many different vaccines would cause at least one person to develop IDDM from a vaccine. This is made more credible by the fact that it is known that people are born with a finite number of islet cells which secrete insulin and that these islet cells decline with time. Glucose tolerance tests and simple fasting blood sugars indicate that a number of people are borderline between maintaining satisfactory glucose control and being diabetic. Further destruction of pancreatic islet cells will lead to the development of diabetes in these patients. It is thus very easy to accept that a challenge with a vaccine could lead to the destruction of some islet cells and the development of overt diabetes in borderline diabetics. It is also easy to accept that since people receive multiple doses of many different vaccines, that the cumulative effect in some individuals would be the destruction of a significant number of islet cell. The support for a causal relationship between vaccines and IDDM is made even stronger by the many different mechanisms **(Section III)** by which vaccines are expected to destroy pancreatic islet cells and cause IDDM.

Animal toxicity data **(Section IV)** and in vitro data provide further proof that vaccines cause IDDM in humans. The pertussis vaccine was associated with an increased risk of IDDM in NOD female mice. Given the similarity between the mouse and human immune system and the fact that billions of people are immunized it is certain vaccines will speed the destruction of pancreatic islet cells in some people as occurs in mice. Further proof of this phenomenon is provided by other animal models of autoimmunity where vaccines exacerbate these autoimmune diseases.

Epidemiology data proving a causal relationship between vaccines and human autoimmune diseases other than IDDM **(Section V)** is strong proof that vaccines can cause IDDM in some people. Autoimmune process involve the attack of self tissue or molecules by the body's own immune system. It has already been proven that autoimmune diseases share common mechanisms and pathophysiology. Data supporting this include families with high incidence of autoimmunity where different members have different autoimmune diseases, linkage of certain high risk genes to several different autoimmune diseases, syndromes where people develop several different autoimmune diseases , and resolution of many different

autoimmune diseases by treatment with the same immune suppressant. Data providing proof that vaccines can induce several different autoimmune diseases is proof that vaccines can and do cause IDDM. Such data includes: hepatitis B vaccine was shown to more likely than not to cause allopecia, autoimmune induced hair loss (1); the original rabies vaccine induced autoimmune neurologic diseases (2) ; and the tetanus vaccine has been used to routinely induce autoimmunity against HCG hormone (3).

Epidemiology data linking natural infections **(Section III)** with autoimmunity especially IDDM provides further proof vaccines cause IDDM. For example the rubella virus is known to cause IDDM. The rubella vaccine is derived by selecting for mutants that are less toxic to humans. However it is inevitable that the vaccine rubella virus will also destroy pancreatic islet cells in some people. This is based on the genetic variability of the billions of people receiving the vaccine and the fact that live vaccine virus can revert back or have the activity of the wild virus in some people.

Direct epidemiology data linking vaccines and IDDM **(Section VI)** is the final proof that vaccines cause IDDM. Many different papers have been written describing how to evaluate epidemiology data to search for proof of a causal relationship between an specific environmental challenge, such as a vaccine, and the development of a specific disease such as IDDM. Formal published criteria (4) for proving a causal relationship between vaccines and an adverse event have been met thus proving a causal relationship between vaccines and IDDM. Several of the points used for proving a causal relationship are summarized in **Table 0A** and specific examples are referenced. Sharp rises in the incidence of IDDM after vaccination were seen in populations where the incidence of IDDM was previous stable for many years prior to the introduction of a vaccine. Sharp rises or "step ups" in the incidence of IDDM in populations after vaccination were also seen in populations where the incidence was rising gradually. A consistent temporal association between vaccination and the rise in IDDM has been demonstrated which ranges from 2-4 years for many vaccines. Congruency between several different types of studies has been demonstrated. Declines in the incidence of IDDM following discontinuation of vaccines are described. Changes in the age of diagnosis depending on the timing of administration of the vaccine have been demonstrated.

The direct epidemiology data linking vaccines to IDDM is helpful in proving causality but is not essential. For example if several different unrelated vaccines are proven to cause IDDM, and either an animal toxicology model is developed or a mechanism of action is established then epidemiology data is not necessary to prove a specific vaccine causes IDDM. All that is necessary to prove causality is knowledge that the vaccine would act by the same mechanism of action or has the same affect in animals as the vaccines already proven to cause IDDM. This is the case with some older vaccines like the polio vaccine. It is hard to perform epidemiology studies because it is hard to find data on large numbers of unvaccinated controls. However, based on their similarities to other vaccines it is certain they would cause IDDM in some people.

The frequency of reporting of vaccine adverse events is not a criteria for proving a causal relationship, however reporting of possible adverse events provides proof for the acceptance that vaccines can cause an adverse event such as IDDM. Furthermore acceptance in the lay press is also proof that many people believe vaccines can cause IDDM. Under reporting is a known problem with trying to determine vaccine adverse events (5). Part of the failure to report vaccine induced autoimmunity is because the autoimmune disease may not occur for many years after vaccination. Cases of autoimmunity induced by rabies vaccines have first become clinically apparent 10 to 20 years after the vaccine was administered (6), at a time when the patients have even forgotten that they had received the rabies vaccine. Cases of Guillain-Barre Syndrome have been reported to occur 4-10 months after vaccination (7). However, when autoimmunity occurs more than one month after immunization physicians often fail to recognize the association. Autoimmunity is a commonly reported adverse event associated with the hepatitis B vaccine in France and IDDM is one of the most common adverse event reported in France. While this does not prove vaccines cause IDDM it does prove that people believe vaccines can cause IDDM.

Therefore it is proven that vaccines can and have induced IDDM. The issue then becomes how many people develop IDDM from immunization and what is the time frame from vaccination and the development of diabetes. Epidemiology data **(Section VII)** is used to quantitate the magnitude of an effect for many different vaccines. This data provides proof that the effect is large.

# II. Type I Diabetes, Insulin Dependent Diabetes Mellitus (IDDM)

### *1. Introduction to IDDM and autoimmunity*

Type I diabetes mellitus, insulin dependent diabetes (IDDM), is a chronic disease of humans with a primary onset occurring frequently in childhood and adolescence. IDDM results from insufficient insulin secretion. Insulin is a hormone that maintains low blood sugar levels and is made in special cells located in the pancreas called islet cells. The onset is often associated with an abrupt occurrence of polydipsia, polyuria, weight loss, fatigue, irritability and typically results in death if insulin therapy is not initiated. Serious chronic complications frequently afflict insulin treated diabetics later in life resulting in expensive hospitalization, loss of employment, and a decline in quality of life.

Any mechanism that destroys islet cells will cause IDDM. It is established that most cases of IDDM are the result of autoimmune disease as discussed below. Autoimmune disease is a process where a patient's immune system attacks their own tissue and destroys it. The immune system contains different white blood cells called B lymphocytes and T lymphocytes. The B lymphocytes produce antibodies which bind to self tissue and destroy the tissue. T lymphocytes can destroy self tissue by direct contact. The environment also has a big effect.

### *2. IDDM is an autoimmune disease*

Substantial evidence has existed for a while suggesting that IDDM is an autoimmune disease. This data has been extensively reviewed in several papers (8-11) so only some of the essential points will be discussed here. Findings suggesting an autoimmune etiology include the presence of insulitis in the pancreas of recently diagnosed type I diabetics along with the presence of islet cell antibodies in early diabetics and prediabetics. Glutamic acid decarboxylase reacts with sera from prediabetics and early diabetics in 70% or more of cases leading some believe that it may trigger the development of an anti-islet cell autoimmune response.

Clinical trials and epidemiological studies have supported an immunological link to IDDM. Treatment of newly diagnosed type I diabetics with cyclosporine can reverse diabetes temporarily (12,13). Epidemiology has shown strong linkage of type I diabetes with the major histocompatability genes that control the development of immune responses. Approximately 95% of Caucasian type I diabetics express MHC class II alleles DR3 or DR4 while these alleles are expressed in only about 40% of the Caucasian population (14). Other studies suggest a protective effect of certain MHC alleles as demonstrated by an inverse correlation between the expression of the DR2 allele and the development of diabetes. Studies of type I diabetes in identical twins show that the concordance rate is less than 50% (15). This finding suggests that genes do not have absolute control on the development of diabetes and that environmental factors have a strong effect also.

Some of the best evidence suggesting diabetics may have an immune disorder include papers showing an increased incidence of classic autoimmune diseases like thyroiditis in type I diabetics (16). That antithyroid antibodies are more common in females but islet cell antibodies and IDDM are equally common in male and female children has raised questions on whether the disorders are casually related or are derived from common immunological defects.

***3. Viral component***

There is also substantial evidence that virus infections alter the risk of IDDM. Infections with rubella virus have been proven to cause IDDM (17-19). Recently data indicates the coxsackie B virus may also cause IDDM (20) (21) (22). The exact mechanism that virus infections induce IDDM is not known. The viruses may initiate destruction of pancreatic islet cells which initiate an autoimmune disease.

***4. Progression of islet cell destruction***

Humans are born with a finite number of pancreatic islet cells and these cells generally can not replicate. Once a person looses about 90% of their islet cells they can no longer maintain their blood glucose and develop IDDM. There is a lot evidence that the islet cells are destroyed over a prolonged period of time (23). Several recent studies have shown that many people classified as type II diabetics may actually suffer from a slowly progressing autoimmune destruction of the insulin secreting islet cells and are really early type I diabetics (24-30).

The destruction of islet cells may not be gradual but may progress sporadically. This is supported by data that titers of autoantibdies to islet cells may fluctuate and may even become undetectable at times (31-34). This indicates certain environmental triggers may cause the anti-islet cell autoimmune disease to flair.

***5. Incidence of IDDM and rises in IDDM***

The risk of developing IDDM varies significantly by country and race. The incidence of IDDM has been rising in many countries indicating environmental factors may be introduced which are increasing the risk of IDDM (35). The incidence of IDDM in the US is rising in children under 20 (36). The mean incidence of IDDM in Pittsburgh in the years 1990-1994 for children under 20 was 16.1 cases/100,000 which represents a cumulative risk of 322 cases/100,000 (36). The rate of IDDM after age 20 in the US non military is estimated to be 9.2 cases/100,000 the cumulative incidence from age 20 to 82 would be 570 cases/100,000 or a life time risk of 890 cases/100,000 (37). This is equal to a life time risk 1 in 112. Furthermore it is estimated that approximately 30,000 people develop type I diabetes (IDDM) in the US each year. This is likely to be a underestimate because many people diagnosed with type II diabetes (NIDDM) have autoantibodies to islet cells indicating they suffer from autoimmune destruction of islet cells and should be classified as type I diabetics (38) (26,27).

### *6. Cost of IDDM*

The American Diabetes Association (24) estimates that combined economic cost of type I and type II diabetes in the United States was $92 billion in 1992 which was due to $45 billion in medical expenses and $47 billion in lost productivity. Patients with type I diabetes make up about 10% of all diabetics which would account for a total cost of at least $9.2 billion annually. Many if not the majority of experts believe that about 10% of those diagnosed with type II diabetes actually have adult onset type I diabetes (26,27), which could attribute another $8.3 billion in costs to type I diabetes. Patients with type I diabetes tend to develop disease much earlier in life and to have much more severe disease than those with type II diabetes. Both effects results in a significant higher cost of disease in type I than type II diabetics. This difference could contribute an additional $10 billion in costs to type I diabetes. The net effect is that type I diabetes costs the United States economy about $28 billion annually. The cost of type I diabetes in western Europe is estimated to be about the same as in the US based on the size of the population, incidence of diabetes, and the quality of health care.

# III. Mechanisms of Vaccine Induced IDDM

## *1. Introduction*

The published literature indicates that immunization starting after 8 weeks of life is associated with an increased risk of IDDM (39). There are several mechanisms by which vaccines are expected to increase the risk of autoimmune diseases including IDDM. Some vaccines contain molecules that immunologically cross react to self molecules so these vaccines are expected to be able to induce an immune response against these self molecules. Vaccines also contain immune stimulants such as aluminum adjuvants and these substances can induce an aberrant immune responses. Vaccines may also induce aberrant immune responses by altering the ratio of Th1 and Th2 lymphocytes. It has been proposed that both the mumps and rubella vaccines may infect the pancreatic islet cells and lead to the development of IDDM. Vaccines may also increase the risk of IDDM by increasing the expression of certain intrinsic viruses.

The most common mechanism by which vaccines are expected to induce autoimmunity is through stimulating the immune system and exacerbating smoldering autoimmune diseases. In this process the vaccines act as adjuvants to induce autoimmunity to self molecules in close association with the foreign vaccine molecules. The pertussis vaccine is known to be an effective adjuvant, stimulating an immune response to agents that are in close association to it (40). Immunization with the tetanus toxoid increases the ability of pregnant women to develop antibodies to the fetus's red blood cells (41).

## *2. Vaccine induced macrophage activity*

Type I diabetics have increased macrophage activity. It is believed that this increased activity precedes the development of IDDM and contributes to the onset of IDDM. Data supporting a causal relationship between macrophage activation and IDDM includes data showing humans at risk for IDDM because of family history have been found to have increased macrophage activity similar to that seen in diabetics (42,43). Animal models indicate that macrophages are involved in the initiation of diabetes (44) Many vaccines activate macrophages and would be expected to increase the risk of IDDM. Vaccines can both directly activate macrophages and indirectly activate macrophages through the release of cytokines. Macrophages are particularly stimulated by vaccine adjuvants including aluminum (45) and complex polysaccharides (46) similar to what are found in certain capsular vaccines like pneumococcal and hemophilus vaccines. Insoluble polysaccharides (46) like those found in vaccines are also more potent activators of macrophages then soluble polysaccharides which may be more common with natural infections.

Macrophages may increase destruction of islet cells by releasing cytotoxic molecules (47,48). Certain macrophages may preferentially increase the replication of Th1 lymphocytes (49) leading to destruction of pancreatic islet cells. Macrophages can injure pancreatic islet cells

through the release of free radicals, nitric oxide, and cytokines including IL-1 and TNF (47). Activated macrophages also release alpha interferon. Alpha interferon has been repeatedly reported to cause IDDM in humans (50-53).

Activated macrophages can increase autoimmunity by presenting self antigens to autoreactive lymphocytes and activating the autoreactive lymphocytes. These autoreactive lymphocytes can kill islets through direct contact with the cells or through the production of soluble autoantibodies which destroy islet cells. The mechanism for inducing autoimmunity appears to involve a lymphokine drive phenomenon where the vaccine activates the immune systems and an immune response develops to autoantigens that are attached to MHC molecules on the same or adjacent antigen presenting cells as the vaccine toxoids. This phenomenon appears to occur in the draining lymph nodes (54,55) and is likely to involve both the direct activation of macrophages (45) , the release of lymphokines capable of inducing autoimmunity (56) and the up regulation of lympokine receptors on cells (57).

### *3. Vaccine induced alpha interferon release on IDDM*

It is generally accepted that vaccines are potent immune stimulants. One mechanism by which vaccines can stimulate the immune system is through the release of interferons. Individuals receiving vaccines develop fevers, fatigue, weakness, headache, sweating, myalgia **(Physician's Desk Reference).** These symptoms are similar to patients receiving interferons including fever, myalgia, headache **(Physician's Desk Reference ).** Many vaccines activate macrophages and macrophages release alpha interferon. Alpha interferon is released from macrophages after activation. Alpha interferon has been repeatedly reported to cause IDDM in humans (50-53). One of 40 patients receiving alpha interferon in a Japanese study developed anti-islet cell antibodies (53). An Italian study found 14 of 11,241 patients receiving alpha interferon developed diabetes mellitus (58).

### *4. Vaccine induced lymphokines other than alpha interferon*

Vaccines can cause the release of lymphokines including interferons, interleukins (IL) and tumor necrosis factor (TNF) which can induce IDDM and other autoimmune diseases. Lymphokines may increase the risk of IDDM by directly killing islet cells, speeding a subclinical inflammatory process, altering development of the immune systems, and influencing thymus selection of lymphocytes. Proinflammatory cytokines including (IL-1, TNF alpha, alpha interferon) and type 1 cytokines (interferon gamma, TNF B, IL-2 and IL-12) have been associated with causing islet cell damage (59). The DTP vaccine has been shown to increase tumor necrosis factor in mice (60-61).

Patients receiving IL-2 and interferons have developed numerous autoimmune diseases including organ specific autoimmune diseases, rheumatoid diseases and IDDM (62-66) . IL-2 (67,68) . IL-1 and TNF are toxic to islet cells in vitro (69,70). TNF is believed to increase inflammation near the islet cells (71) while interferon gamma and IL-6 are believed to be involved in the progression from inflammation to autoimmunity (72). The combination of TNF and gamma interferon increases MHC class II molecules on islet cells which is expected to increase the progression of autoimmunity (73). IL-2 enhances an smoldering autoimmune process but is unable to induce an primary autoimmune response (74).

***5. TH1/TH2 ratio altered***

Vaccines may also alter the ratio of Th1 and Th2 lymphocytes (75). T helper 1 (Th1) lymphocytes release gamma interferon, IL-2 and TNF. T helper 2 (Th2) cells release IL-4, IL-5, IL-6, IL-10, IL-13. Th1 activity is associated with destruction of islet cells while Th2 activity is not (76,77).

***6. Increase in autoantibody titers***

Autoantibodies to islet cells have been proven to cause IDDM (26,27,31-33). Vaccines have been proven to nonspecifically increase unrelated autoantibdies presumably through immune stimulation (78-81). It is thus expected that vaccines would increase the risk of IDDM.

***7. Adjuvant effect***

Several investigators working on vaccines to control fertility used the diphtheria and tetanus toxoids, the chief components of the tetanus and diphtheria vaccines, to induce autoimmunity to human chorionic gonadotropin (HCG), in humans. In these experiments the HCG molecule was chemically linked to the diphtheria or tetanus vaccine (3). The ability of vaccines to induce autoimmunity to self antigens that associate with the vaccine molecules can explain the development of a number of autoimmune diseases following immunization.

Vaccines to prevent pregnancy which act by inducing an autoimmune response to HCG have been used in at least four human clinical trials (3). These vaccines consist of human HCG holoprotein or peptides covalently bound to either a diphtheria or tetanus toxoid, the chief component of the diphtheria and tetanus vaccine. The vaccine toxoids were successful in inducing autoimmunity to the human hormone as demonstrated by the development of anti-HCG autoantibodies in the recipients. Detailed studies in animals show that the association of beta HCG with vaccine toxoids greatly increase the immune response to HCG as does the use of alum based adjuvants which are commonly used in vaccines (82). The ability of the vaccines antigens to induce autoimmunity is not limited to HCG since a vaccine comprising a diphtheria toxoid covalently linked to a peptide from human gastrin molecule was able to induce antigastrin antibodies in humans (83)

Animal and human experiments show that vaccine antigens, in killed vaccines, do not have to be covalently attached to autoantigens to induce an autoimmune response. Autoimmunity to the testis and thyroid have been induced in both humans and animals when autoantigens have been administered with Freund's complete adjuvant, (84,85). Autoimmunity has been induced in animals when Freund's complete adjuvant and the autoantigen are administered in different locations but share the same draining lymph nodes (54,55). Animal studies of this phenomenon show the induction of autoimmunity is not limited to the use of Freund's complete adjuvant. For example the administration of the swine flu vaccine in combination with an neural extract has lead to the development of autoimmune neuritis and the administration of the pertussis vaccine with thyroid extract has lead to the development of autoimmune thyroiditis in rodents (86,87) . In the later case a depot type adjuvant, Freund's incomplete adjuvant, was necessary for the induction of autoimmunity. Administration of the pertussis vaccine in the absence of autoantigens has been shown to exacerbate smoldering autoimmunity in rodents (88).

The ability of vaccines to induce an autoimmune response to antigens that are in proximity to them explains the induction of autoimmunity in humans following immunization. Vaccine antigens become closely associated with immunoglobulins after entering the body and this explains why rheumatoid factor, an autoantibody against IgG antibodies, frequently develops after immunization (89-92). Antigens from killed vaccines associate with a number of other autoantigens besides IgG after being administered. For example antigens from the DTP and other killed vaccines are known to circulate in the blood stream (93) and associate with the membranes of blood cells causing acute lysis of these cells (94,95) . This explains why some who receive vaccines develop an autoimmune response to these cells (96-98). Solid organs may also be effected as well. Vaccination causes myocarditis in up to 3% of health patients (99,100) . Part of this can be explained by circulating antigen precipitating in the heart tissue however people often develop autoantibodies to myocardial tissue after damage to the heart (101) and this response can be exacerbated by a vaccine draining into a lymph node where the autoimmune process is developing. In either case the myocarditis induced by vaccination can lead to chronic autoimmune destruction of the myocardial tissue.

Animal studies indicate that if the recipient has a smoldering autoimmune disease that the vaccines do not have to be closely associated with autoantigens to exacerbate disease (88). This is especially troublesome since subclinical autoimmunity occurs in at least 2-3 % of children based on the presence of autoantibodies (28) and autoimmunity is even more common in adults.

***8. Molecular mimicry***

Previous research on vaccine induced autoimmunity focused on vaccines containing molecules that immunologically mimic autoantigens. These foreign antigens induce antibodies that cross react to self antigens. One example is the neural tissue derived rabies vaccine which contained neural antigens that induced an autoimmune encephalitis in recipients (2). The whole

cell pertussis vaccine (102) and the BCG vaccine (103) contain heat shock proteins that cross react to pancreatic islet cell proteins and may induce IDDM. Molecular mimicry however does not explain the variety of autoantibodies that arise after vaccination (78-81). This indicates vaccines may alter autoimmunity by antigen nonspecific mechanisms as discussed above.

*9. Natural infections*

Natural infections are known to increase the risk of IDDM (104,105). Therefore it is expected that vaccines would increase the risk as well. Humans suffering from natural immune suppression are at increased risk for developing autoimmune diseases (106,107) and some vaccines (108) have been associated with immune suppression. Vaccination induced immune suppression could lead to an altered risk of IDDM, possibly by allowing chronic infections with certain diabetes causing viruses. Vaccines may also lead to an increased risk of IDDM by eliminating natural infections which prevent immune mediated disorders (109). Living in a more sterile environment may increase the risk of diabetes in humans (110) and rodents (111).

*10. Vaccine induced viral release and IDDM*

Immunization with the tetanus (112), hepatitis B, and influenza vaccine have all been shown to cause blood viral titers to increase in patients with HIV (113). The mechanisms include increased viral replication and release (114) . The phenomenon does not appear to be specific for HIV and thus persons persistently infected with other viruses are likely to have a similar effect. It is thus probable that in individuals chronically infected with certain IDDM causing viruses that vaccines could cause the multiplication and or release of these viruses into the blood which could then infect islet cells. The rubella virus is known to cause IDDM (17-19) and there is now evidence that other viruses can cause IDDM, in particular coxsackie B viruses. It is thus likely that in some people infected with viruses that vaccines make the viral infection worse and leads to IDDM.

Data has been published indicating that type I diabetics in a country tend to be born more frequently in certain months (104). This can be explained by viral infections of the newborn or pregnant mother during these months since certain viral infections tend to be epidemic in certain months. This theory is based on data that congenital rubella infections lead to an increased risk of IDDM (17-19).

Dahlquist (20) and others (21) have shown that viruses beside rubella, in particular enteroviruses, are likely to cause IDDM through the same infectious route. Vertically transmitted Coxsackie B virus infections which have been attributed to causing 27% or more cases of insulin dependent diabetes (20). Dahlquist (22) presented additional data from her studies on maternal infections and the risk of IDDM.

Vaccines may also stimulate the expression of retroviral antigens on the surface of islet cells or macrophages leading to an immunological attack against the pancreatic islet cells. A retroviral gene in humans, associated with the development of IDDM, codes for a super antigen (115) . Super antigens cause polyclonal lymphocyte activation and polyclonal activators have been associated with an increased risk of autoimmunity. Vaccination after 2 month of life may cause the expression of this retroviral antigen leading to the development of IDDM while vaccination at birth may cause expression at birth leading to immunological tolerance and prevention of IDDM.

### *11. Live vaccines*

It has been proposed that both the mumps and rubella (18,116,117) vaccines may infect the pancreatic islet cells and lead to the development of IDDM. Rubella infections (17-19) are known to cause IDDM and many believe that mumps infections also cause diabetes (118). It is proposed that the rubella and mumps vaccine viruses resemble the natural viruses or revert back to the wild virus enough to cause IDDM. The best supporting data for a direct infection of islet cells comes from data showing the rubella virus can infect islet cells grown in culture (19). Proof that the vaccine virus can induce diabetes just as the wild virus can is provided by findings that other live attenuated vaccines cause diseases resembling the wild virus in some patients. This has been documented with the polio, smallpox , BCG, chickenpox, and rotavirus vaccines.

### *12. Cell toxins*

Certain vaccines may contain impurities such as contaminating viruses and preservatives that may be directly toxic to the islet cells. Thimerosal a vaccine preservative is known to be cytotoxic.

### *13. Decrease natural infections, cleanliness*

There is data that natural infections may prevent diabetes (110) and other autoimmune diseases. Vaccination may alter timing of exposure to natural infection and hence increase the risk of autoimmunity (119) (109).

### *14. Difference between natural infections and immunization*

Vaccines differ from natural infections in several respects so it is understandable that they have different affects on the development of IDDM. While naturally acquired foreign antigens such as infections (120) may also lead to induction of autoimmunity, animal and human experiments have shown the use of depot type adjuvants as well as repetitive administrations intensifies the induction of autoantibodies (3,82). Vaccines are often given intramuscularly while infections often occur on the surface of a mucous membrane. The recipient of a vaccine is

exposed to a large bolus of immunogens at once while in natural infections exposure to immunogens occurs more gradually as the pathogen replicates on the surface of a mucous membrane and the immunogens slowly cross the mucous membrane barriers. Children may receive vaccines against 5 or more diseases at one time while it is highly unusual for a child to develop more than one of these infections at one time.

All of these differences would be expected to cause differences in the secretion of corticosteroids by the adrenal gland. The adrenal gland is one of the body's key system to prevent autoimmunity. Adrenalectomy has been shown to exacerbate autoimmunity in both humans (121) and rats (122). Adrenal corticosteroids by contrast are used to treat almost all autoimmune diseases. It takes about 3 days for the adrenal glands to increase production of corticosterioids . This time frame is adequate for preventing exacerbations of autoimmunity following infections because it takes several days for the infection to invade the host, multiply to large numbers and stimulate the immune systems. By contrast the adrenal gland is not well suited for preventing autoimmunity following vaccines because the immune system is exposed to large amounts of immunogen immediately following immunization and the immune stimulation occurs quickly.

# IV. Animal Toxicology Studies

## 1. Introduction

Nonobese diabetic, NOD, mice spontaneously develop insulin dependent diabetes and are a model of human IDDM. Disease in these animals, as in humans, is of an autoimmune etiology that is heavily influenced by both genetics and environment. Substantial evidence exists that observations made in these animals have potential clinical relevance to human IDDM. Much of this data has been reviewed in several recent publications (123-125) so only a few key points are discussed below.

There are many similarities between diabetes in NOD mice and humans. Disease onset occurs commonly in young mice which develop hyperglycemia, glycosuria, polyuria, ketonuria, hypoinsulinemia and death results in 1-2 months if the mice do not receive insulin. Insulitis develops in the pancreas before the development of diabetes. Animals develop glutamic acid decarboxylase autoantibodies, insulin autoantibodies and islet cell autoantibodies. Diabetes can be prevented by the administration of immune suppressants like cyclosporine during the prediabetic period. Genetic experiments show that diabetes is closely linked to the MHC class II genes in NOD mice as it is in humans. Some NOD mice develop autoimmune thyroiditis that is casually related to the development of diabetes (126,127).

Experiments have been performed in NOD mice to provide further evidence supporting an autoimmune etiology of insulin dependent diabetes. Diabetes can be passively transferred by purified lymphocytes while neonatal thymectomy or anti-lymphocyte antibodies can prevent diabetes. Purified lymphokines like TNF, and IL-1 can also prevent diabetes (128,129). Researchers have found evidence of retroviral particles in the beta cells of NOD mice that may explain the initiation of the insulitis (130,131).

Attempts have been made at locating immunological disorders in the NOD mice that predispose them to develop diabetes. The most profound defect is the failure of the mice to express the MHC class II I-E alleles. There is data suggesting total number of lymphocytes may be transiently reduced in NOD mice before 160 days (127). Data also exists that there may be a defect in Lyt-2 "suppresser" cells (132)

The similarity between diabetes in the NOD mice and humans is extensive however the influence of sex on the incidence of disease is a striking difference. The incidence of diabetes in female mice at 6 months is about 80% compared to 20% in males. This difference is not seen in all substrains of NOD mice however it occurs in most strains throughout the life of the animals. The sex difference can be explained by a sensitivity of the immune system to sex hormones. Castration increases the incidence of diabetes in male mice, ovarectomy decreases the incidence in female mice, while administration of testosterone decreases the incidence of diabetes

(133-135). Male sex hormones may be exerting an inhibitory effect on lymphocytes because thymectomy on day 3 of life increases the incidence of diabetes in males and decreases difference in incidence between the sexes (136).

### *2. Vaccines cause inflammation of rodent pancreas*

Goto et al. described experiments showing that injections of guinea pigs with several different vaccines containing aluminum adjuvant caused inflammation in the pancreas (137). The amount of inflammation in the pancreas correlated with inflammation at the injection site.

### *3. Pertussis vaccine in female NOD mice.*

Several experiments (138) were designed to study the effect of administering a single injection of DTP vaccine after 2 months but before 4 months of age, as is common in the United States. A group of 30 female NOD mice that received 1 injection of the DTP vaccine at 8 weeks (.2 ml, 1:50) developed a cumulative incidence of diabetes of 86.7% by 32 weeks of life. This incidence was higher than several different control groups receiving saline including a group of 27 female mice followed for 32 weeks of life (48%) and a group of 20 female mice followed for 28 weeks (65%) and 36 weeks (75%). **(Table 1A , Figure 1A)**

A second experiment was designed to see the effect of administering a single dose of the whole cell pertussis vaccine at 8 weeks of life to a group already receiving the anthrax and DT vaccines starting at birth. Only 7.7% of female NOD mice receiving the combination of the anthrax and DT vaccines (n=26) starting at birth developed diabetes by 32 weeks while 23% of mice developed diabetes (P=0.065) in a group receiving an identical treatment except the DTP vaccine was administered in place of the DT vaccine at week 8 (n=26) . **(Table 1A, Figure 1A)**

### *4. Related autoimmune diseases*

Animal studies below show that human vaccines can induce autoimmunity when administered with autoantigens, exacerbate autoimmunity when given alone, and can induce autoimmunity when administered without autoantigens. Freund's complete adjuvant, which contains BCG or a similar mycobacterium in mineral oil, when mixed with autoantigens is one of the strongest inducers of autoimmunity known. BCG vaccine is also been shown to exacerbate autoimmunity in lupus prone mice (139). The pertussis vaccine has been shown to be an adjuvant for a number of autoimmune diseases. The administration of the pertussis vaccine with thyroid extract in Freund's incomplete adjuvant caused the development of autoimmune thyroiditis in rats (140). The addition of pertussis vaccine also exacerbated autoimmune thyroiditis induced in rats by the administration of thyroid extract in Freund's complete adjuvant (141). Autoimmune nephritis (142) and sialadenitis (143) have been induced in guinea pigs with pertussis vaccine and tissue homogenates. Streptococcal vaccines have been shown to induce a number of autoimmune diseases in rabbits (144-146).

The pertussis as well as other vaccines have been shown to induce demyelinating autoimmune diseases in rodents. Administration of pertussis vaccine with homogenized spinal cord caused the induction of experimental allergic encephalitis, EAE, in rats (55). Administration of the pertussis vaccine in the absence of autoantigens has been shown to exacerbate smoldering EAE in rats (88). Administration of the swine flu vaccine in combination with an neural extract has lead to the development of autoimmune neuritis (86). Live attenuated vaccines including measles, rubella, BCG and distemper vaccines have been shown to exacerbate EAE in Guinea pigs induced by the administration of homologous spinal cord in Freund's complete adjuvant (147).

## V. Related Epidemiology Studies

### *1. Introduction*

The effect of vaccines on the risk of developing an autoimmune diseases other than IDDM has not been well studied with a few notable exceptions. To perform an study ideally one needs 80,000 or more vaccinated children and 80,000 or more matched controls. The children need to be followed for 10 years and a system needs to be in place to accurately record cases of autoimmunity as they occur. The later difficult for many autoimmune diseases since the onset is gradual and there may not be a clear cut definition of the disease that can be rapidly ascertained when screening the medical records of 160,000 or more people. IDDM by contrast is easier to measure because the cases can be ascertained by the administration of insulin or the presence of hyperglycemia. While it is difficult to perform clinical trials to study the risk of autoimmunity following immunization there is data to prove vaccines cause different autoimmune diseases in humans and thus it is inevitable vaccines are also causing IDDM.

### *2. Clinical trials*

#### *2A. Fertility vaccines*

Vaccines to prevent pregnancy which act by inducing an autoimmune response to HCG have been used in at least four human clinical trials (3). These vaccines consist of human HCG peptides covalently bound to either a diphtheria or tetanus toxoid, the chief component of the diphtheria and tetanus vaccine. The vaccine toxoids were successful in inducing autoimmunity as demonstrated by the development of anti-HCG autoantibodies in the recipients

#### *2B. Cancer vaccines*

Autoimmunity to the testis and thyroid have been induced in both humans and animals when autoantigens have been administered with Freund's complete adjuvant, (84,85). Freund's complete adjuvant uses the BCG vaccine to induce autoimmunity.

#### *2C. Pneumococcus vaccine trial*

On November 5, 1999 Wyeth-Lederle presented data to the FDA's Vaccine and Related Biological Products Advisory Committee on their pneumococcal 7-valent conjugate vaccine, diphtheria CRM protein. The final formulation contains two micrograms of each of six types, and four micrograms of type 6b polysacharide. The formulation includes a total dose of 20 micrograms of CRM and .5 milligrams of aluminum phosphate. The study was performed by Kaiser Permanente and involved 37,868 children which were either assigned to receive the 7-valent pneumococcal conjugate or a meningococcal c conjugate vaccine. There were a total of

22 cases of autoimmunity including IDDM in the meningococcal vaccine group and 12 in the pneumococcal vaccine group after less than 3 years of follow up ***P=0.086*** (Chi Square).

### *3. Epidemiology studies*

#### *3A. Hepatitis B vaccine*

The hepatitis B vaccine has been associated with an increased risk of a number of different autoimmune diseases. The FDA has published data showing loss of hair, an autoimmune disease called alopecia, occurred in children after receiving the hepatitis B vaccine (1). The study found 46 cases of alopecia following hepatitis B immunization. In 15 cases the hair regrew and the patients received another dose of the vaccine only to have their hair fall out again. The reproducibility of the symptom, hair loss, following rechallenge with the vaccine is considered by the authors as evidence that the vaccine was more likely than not to be causing the autoimmune disease. The delay between immunization and the onset of hair loss was as short as 10 days in a patient who developed hair loss after 2 different doses of hepatitis B vaccine. This indicates that that vaccine induced autoimmune disease can occur within weeks of immunization.

#### *3B. Rabies vaccine*

The old neural tissue derived rabies vaccine contained neural antigens that induced an autoimmune encephalitis in recipients (2). Cases of autoimmunity induced by rabies vaccines have first become clinically apparent 10 to 20 years after the vaccine was administered (6), at a time when the patients have even forgotten that they had received the rabies vaccine.

#### *3C. Guillain-Barre syndrome*

Cases of Guillain-Barre Syndrome, an autoimmune neurological disease, have been reported to occur 4-10 months after vaccination (7) however when autoimmunity occurs more than one month after immunization physicians often fail to recognize the association.

# VI. Direct Epidemiology Data Linking Vaccines to IDDM

## *1. Introduction*

There is extensive epidemiology that consistently links several different vaccines to the development of IDDM. The data below provides proof that the hemophilus influenza, BCG, mumps-rubella, pertussis, and hepatitis B vaccine cause IDDM. Data supporting a causal relationship between several other vaccines and the development of IDDM is also included. Vaccines which have recently entered the market have been easier to study for their affect on IDDM because there is data on a large number of unimmunized children. It is difficult to perform epidemiology data on some older vaccines such as the polio vaccine since it is difficult to find data on large groups of unimmunized children.

## *1A. Criteria supporting a causal relationship*

Many different papers have been written describing how to evaluate epidemiology data to establish proof of a causal relationship between an specific environmental challenge , such as a vaccine, and the development of a specific disease such as IDDM. An paper was written by researchers attempting to determine if a causal relationship exists between the MMR vaccine and autism (4). Several of the points used for proving a causal relationship are summarized in **Table 0A** and specific examples are referenced. Data from a prospective clinical trial with a HiB vaccine supports a causal relationship. Sharp rises in the incidence of IDDM post immunization were seen in populations where the incidence of IDDM was previous stable for many years before the introduction of a vaccine. Sharp rises or "step ups" post immunization were also seen in the incidence of IDDM in populations where the incidence was rising gradually. A consistent temporal association between vaccines and the rise in IDDM has been demonstrated which ranges from 2-4 years for many vaccines. Congruency between several different types of studies has been demonstrated. Declines in the incidence of IDDM following discontinuation of vaccines has occurred. Differences in the incidence of IDDM depending on the timing of administration of a vaccine have been demonstrated.

## *1B Time delay between vaccination and IDDM; clustering*

One method of proving causality is to demonstrate clustering of cases of IDDM at a specific interval following immunization. Sultz et al. (148) published epidemiology data that there was a 3 to 4 year delay between mumps epidemics and IDDM epidemics. The authors described a median lag time of 3 years and a median lag time of 3.8 years between the infection with mumps and the development of IDDM. A median lag time of 3 years implies a number of cases occurring before 3 years. They also employed 3 year averages in their calculations with IDDM. A clinical trial on the hemophilus vaccine **(Section VI, 2A)** randomized children to receive 4 doses of vaccine starting at 3 months of life or a single dose given at 2 years of life. The incidence of IDDM in the two groups separated at about 3.5 years and then became parallel

**(Figure 2B)** . This is also consistent with about a 3 to 4 year delay between insult (i.e. vaccination) and the development of IDDM. It is also strong proof of a causal relationship. Based on these findings the data below was analyzed assuming a 3 to 4 year delay between vaccination and the development of IDDM. Steep rise in the incidence of IDDM occur between 2-4 years following the addition of several different vaccines including the hemophilus **(Section VI, 2)**, hepatitis B **(Section VI, 3)**, mumps rubella **(Section VI, 5)**, and pertussis vaccines **(Section VI, 6)**. This data, described below, is consistent with clustering and provided proof of a causal relationship.

### *1C. Age of diagnosis of IDDM altered by vaccines*

The existence of changes in the age of diagnosis of IDDM after the addition of a new vaccine to the immunization schedule provides proof of a causal relationship. The repetitive addition of new vaccines to the immunization schedule is associated with a trend to an earlier onset of IDDM in addition to the trend for an increase in incidence of IDDM. The rise in the incidence of IDDM is occurring primarily in the younger age children who are receiving the new vaccines. This phenomenon has been documented in Finland (149) and many other countries in Europe (150) and around the world (35).

### *1D. Effect of timing on the development of IDDM*

Consistent correlation between risk of IDDM and the timing of administration provides proof of a causal relationship. Immunization starting at school age with the BCG vaccine is highly associated with an increased risk of IDDM **(Section VI, 4)** while immunization starting at birth is associated with an decreased risk of IDDM.

### *1E. Congruency between several different types of studies.*

Congruency between several different studies and particularly several different types of studies provides proof of a causal relationship. Demonstration of a consistent rise in IDDM in vaccinated cohorts compared to historical controls provides strong evidence for a causal relationship however this is made even stronger by similar results from case control studies using age matched contemporary controls. Congruent data from several different studies exists for many different vaccines as described below. With the hemophilus vaccine **(Section VI, 2)** and rubella **(Section VI, 5)** vaccine there is data from case control studies and autoantibody studies which is congruent with the cohort and ecological data.

### *1F. The rapid decline in IDDM following discontinuation of vaccine*

A rapid decline the incidence of IDDM following discontinuation of a vaccine provide further proof of a causal relationship. Data exists for large statistically significant declines in the incidence of IDDM following the discontinuation of the BCG vaccine **(Section VI, 4C)**

*1D. Methods of analysis.*

The year to year incidence of IDDM fluctuates in any given region and researchers routinely average the incidence of IDDM from 3 or more years to determine a baseline incidence of IDDM (151), (152), (148), (153). The calculations below pertaining to rises of the incidence of IDDM following immunization utilize this process of averaging the incidence of IDDM over 3 years or more.

Rises in the incidence of IDDM have been noticed by individuals who were unaware of the causal relationship between vaccines and IDDM (150). These individuals have described rates of increases in the incidence of IDDM in different countries. These authors have suggested a linear rise in the incidence of IDDM. The analysis below however shows that the changes in the incidence of IDDM in many different countries can be better described by a series of sharp rises following the introduction of a new vaccine and then a plateau until a new vaccine is added to the immunization schedule. The sharp rises in IDDM occurring following immunization can not be explained by underlying linear rises in the incidence of IDDM in the countries studied below.

*2. Hemophilus vaccine*

*2A. Hemophilus vaccine: Finland*

The effect of the Hemophilus influenza vaccine on the development of IDDM (154) was studied in Finland. The study followed up on a clinical trial (155). All children born in Finland between October 1st, 1985 and August 31st, 1987, approximately 116,000, were randomized to receive 4 doses of the HiB vaccine (PPR-D, Connaught) starting at 3 months of life or one dose starting at 24 months of life. By design of the original study, historical controls were designated as the unvaccinated controls for long term safety studies. An intent to treat method was used to calculate the incidence of IDDM in both treatment groups until age 10. The incidence of IDDM was also calculated in an control group which did not receive the HiB vaccine, a cohort which included all 128,500 children born in Finland in the 24 months prior to the HiB vaccine study. Cases of IDDM were collected as part of a prospective registry (156).

The results are described in detail below **(Table 2A; Figure 2A, 2B, 2C, 2E).** The cumulative incidence of IDDM/100,000 in the groups receiving 4, 1, and 0 doses of hemophilus vaccine were 398, 376, 340 at 10 years of age respectively. The difference in cumulative incidence between those receiving 4 doses and those receiving 0 doses was 58 cases IDDM/100,000 at 10 years (P=0.029) using a single tail Fisher test. The relative risk was 1.17 at 10 years. The cumulative incidence of IDDM/100,000 in the 3 groups were 261, 237, 207 at 7 years respectively. The difference in cumulative incidence between those receiving 4 doses and those receiving 0 doses was 54 cases of IDDM/100,000 (P=0.013) at 7 years. The relative risk

equaled 1.26 at 7 years. The difference in cumulative incidence between those receiving any vaccine (4 or 1 doses) and those receiving 0 doses was 42 cases IDDM/100,000 (P=0.016) at 7 years and 47 cases at 10 years (P=0.028). The relative risks were 1.2 and 1.14 at 7 and 10 years respectively.

The group receiving 4 doses of HiB vaccine had 22 cases of IDDM/100,000 more than the single dose group and the curves separated between 3 and 4 years of life then became almost parallel for the next 6 years **(Figure 2B)**.

The data shows a statistically significant association between the hemophilus vaccine and an increased risk of IDDM. This data in conjunction with other published information prove a causal relationship between the hemophilus vaccine and IDDM. IDDM had risen in Finland prior to the introduction of the hemophilus vaccine however an underlying temporal rise can not explain the association between the hemophilus vaccine and IDDM described above for several reasons. First the annual incidence of IDDM in the age group 5 through 9 had been stable (156), (149) at approximately 39 cases/100,000/year from 1983-1993 **(Figure 2C)**. This incidence is almost identical with what was found in the unvaccinated group, an average incidence of 40 cases/100,000/year (200/5) . By contrast the HiB vaccinated groups had an average incidence of 46 cases/100,000/year over these 5 years (232/5). Further follow-up of the ecological data shows the incidence of IDDM in the 5-9 age group stabilized at approximately 47 cases/100,000 (range 46.5-48.3) between the years 1994-1996 (149). This demonstrates the rise in IDDM was specific for the vaccinated cohort and the rise in the ecological data followed the rise in the vaccinated group.

There was a previous rise in the incidence of IDDM in the 1-4 year old age group prior to the introduction of the hemophilus vaccine (156) but again this does not explain the association between the hemophilus vaccine and IDDM described above. The group receiving 4 doses, received vaccine starting at 3 months of life while the group receiving 1 dose received the vaccine at 2 years of age. The cumulative incidence of IDDM in these two groups was identical until about 3.5 years of age when there were more cases of IDDM in the group receiving 4 doses. This suggested a delay between vaccination and the development of IDDM of about 3.5 years with the PRP-D based HiB vaccine, in children immunized starting at 3 months. Assuming this same time delay also occurs when the vaccine is given at 2 years of life a difference between the group receiving 1 dose and the unvaccinated group would not be expected before age 5 years. In fact a difference in cumulative incidence of only 6 cases/100,000; 146 versus 140 cases/100,000, was found between the group receiving one dose and the group receiving 0 doses **(Table 2A).** This is the total maximum effect that may not be readily explained by the hemophilus vaccine.

Following the introduction of the hemophilus vaccine the incidence of IDDM in the 1-4 age group stabilized at approximately 34.8 cases/100,000 (range 33.6-35.6) in the years 1994-1996 (149) which is only slightly higher than the 33.2 cases/100, 000 (166/5) which was seen in the group receiving 5 doses of the PPR-D HiB vaccine **(Figure 2D, 2E)**. Just as in the 5 through 9 age group, the incidence in the ecological analysis followed the rise in the vaccinated

group. As with the 5-9 age group, the small additional rise in the incidence of IDDM above that seen with the PRP-D HiB vaccine can be explained by the introduction of more potent vaccines. In Finland a more potent HiB vaccine, the HbOC was introduced 1988, and then starting in 1990 all infants were given still more potent PRP-T (157). The more potent PRP-T vaccine was associated with a relative risk of 1.24 in children under age 5 and 1.20 relative risk in children under age 10.

The data from the hemophilus vaccine clinical trial shows specific temporal clustering of the extra cases of IDDM between the prospectively randomized group receiving 4 and 1 dose of vaccines and this provides proof of a causal relationship **(Table 2B, Figure 2Bi)**. The tabular data shows that there is a numerical difference between groups receiving 4 and 1 dose of vaccine of 22 cases/100,000 by age 10. This difference had been stable since age 5 when the cumulative incidence of IDDM between the two groups was 20 cases/100,000. **Table 2A** shows that all the differences between the cumulative incidence of IDDM between the two groups occurs between ages 2 and 5. Furthermore, **Figure 2Bi** shows that the curves separate between 3 and 4 years of age then become parallel. Essentially all the difference between the cumulative incidence curves of the 4 and 1 dose curves is clustered and occurs during an approximate 6 month period between ages 3 and 4. Analysis of this cluster by tabulating the graphical data **(Figure 2Bi, Table 2B)** indicates there are an extra 11 cases in the group receiving 4 doses during an approximate 3.25 month period and an extra 14 cases in a approximate 5.75 month period. This cluster is statistically significant ($p=0.02$) and provides proof of a causal relationship.

The data also confirms an identical and statistically significant cluster in the group receiving 1 dose of vaccine at 2 years of life. **Figure 2Bii** shows the cumulative incidence of IDDM curves for the group receiving one dose of HiB vaccine and the control group receiving 0 doses. The curves had minor separation prior to 5 years of age, which can be explained by the use of historical controls, however the curves became superimposable between ages 5 and 5.5 years. Around 5.5 years of age (3.5 years after immunization) a cluster of extra cases of IDDM occurred in the group receiving 1 dose of HiB vaccine. Essentially all the cases in the cluster occurred within a six month period and then the curves became parallel. This cluster is essentially identical to what occurred in the group receiving the HiB vaccine at 3 month of age. In both cases the clusters occurred approximately 3.5 years after immunization and were limited to a 6 month period. In both cases the curves became parallel after the cluster. In both cases the clusters were statistically significant. **Table 2A** shows that there is a statistically significant cluster ($p=0.048$) between age 5 and 7 where the incidence of IDDM in the group receiving 1 dose increases over the unvaccinated control by 24 cases/100,000. By contrast the curves only separate by 6 cases between ages 7 to 10, the later can be explained by random variation. The cluster is much more statistically significant than shown in **Table 2A**, because the table assumes the cluster occurred over 2 years when it really occurred over about 6 month, thus greatly increasing the statistical significant. Analysis of this cluster by tabulating the graphical data indicates a high statistical significance ($p=0.002$).

### *2B. Hemophilus vaccine: UK*

The hemophilus influenza B vaccine (PRP-T) was offered to infants in the Oxford regions of the UK starting May 1, 1991 in three of the region's eight districts and July 1, 1991, in a fourth district. Over 90% of infants had been immunized by October 1, 1992 (158). Starting in October of 1992 the vaccine was offered to all children under 5 in the UK (159). The incidence of IDDM rose 33% acutely in the Oxford region in children under age 5 starting in 1994 (160) and continued through 1995 **(Table 5A, Figure 2F)**. This follows the same approximate 3 year delay between immunization with the hemophilus vaccine in Finland and the rise in IDDM.

The incidence of IDDM also rose in Yorkshire, UK following the introduction of the vaccine in 1992 **(Table 5A)**. The incidence of IDDM in children age 0-4 was stable in Yorkshire from 1990 through 1994 at approximately 10 cases/100,000 **(Figure 2G)**. Routine inoculation with the hemophilus vaccine was started in 1992 and a rise in the incidence of IDDM can be seen in 1995, consistent with a 2-4 year delay between immunization and the development of IDDM. The incidence of IDDM after hemophilus vaccination reached 13.5 cases/100,000 in 1998. In the 5-9 year age group a rise in IDDM did not occur until around 1997 which can be explained by a delay between vaccination and the development of IDDM (2-4 years) and the delay it took for those immunized to reach the age of 5 and older **(Figure 2I)**.

The incidence of IDDM in Devon and Cornwall (153) in children age 0-4 rose from 8.89 cases/100,000 (1985-1989) to 14.33 (1990-1996 ) a 61% rise, after the introduction of the hemophilus and the MMR vaccine **(Table 5A, Figure 2H)**. The measles vaccine was replaced by the MMR vaccine in the UK in 1988 and given to children around age 2 in the UK and is expected to have an additive effect with the hemophilus vaccine on the incidence of IDDM explaining the rise seen in Devon and Cornwall (153).

### *2C. Hemophilus vaccine: US*

Drastic rises in the incidence of IDDM have also been reported in the US after the introduction of the HiB vaccine. An epidemic of diabetes in the 0-4 age group occurred during the years 1985-1989 in Allegheny county (161) at a time when the Hemophilus influenza vaccine was being incorporated into the immunization schedule. The FDA approved the Hemophilus influenza polysaccharide vaccine in 1985 and the conjugated vaccine in 1987. The vaccine was widely administered to children in Allegheny county, a study of its efficacy performed in Allegheny county showed that about 36% of children, chosen as controls, were immunized with the vaccine between August of 1985 and July of 1987 (162). The annual incidence of IDDM in 0-4 year old white children living in Allegheny county rose 30% from the years 1980-1984 ( 9.9 cases/100,000) to 1985-1994 (12.8 cases/100,000). The incidence of diabetes in 0-4 year olds had been consistently below 10 cases/100,000 from 1965-1984 (161).

**(Table 2C, Figure 2M)**. The difficulty with the US site is that immunization rates are not known and there is confounding effects from other vaccines such as the hepatitis B vaccine.

### *2D. Hemophilus vaccine: case control study*

A seven center collaborative study looked for an association between vaccines and the development of IDDM (105). The study involved 900 diabetic children and 2,302 controls. The results showed that the hemophilus vaccine was associated with an odds ratio of 1.16 (105). This compares to the relative risk of 1.17 with the hemophilus vaccine in Finland as described above **(Figure 2N)**.

### *2E. Hemophilus vaccine: antibody data*

Graves et al (163) published a study measuring the development of autoantibodies following hemophilus vaccination. Her study design was quite different than the study in Finland described above. In the Finish study an increased rate of 58 cases of IDDM/100,000 by age 10 was found in the group vaccinated starting at 3 months. The extra cases did not begin to occur until about 3.5 years post immunization. By contrasts Graves relied on a single autoantibody to predict the development of IDDM, and it is well known that a single autoantibody has very low specificity for predicting the development of IDDM. The analysis of Finnish children involved studying over 100,000 vaccinated children and an equal number of controls. Graves by contrast studied only 25 individuals with an autoantibody and 292 controls. Graves' study group has only found 5 antibody positive children who developed IDDM while the Finnish study involved 886 cases of IDDM. However, even with all these limitations Graves' found the hemophilus vaccine associated with an relative risk of 1.27 (72/62, Graves' Table 1). These results are almost identical to the relative risk of 1.19 at age 5, 1.26 at age 7, and 1.17 at age 10 for the children receiving 4 doses of hemophilus vaccine in Finland **(Figure 2N)**.

### *2F. Hemophilus vaccine: additional countries*

Rises have been reported in Australia, Sweden (personal communication Harold Heijbel), Iceland **(Figure 2K)**, New Zealand **(Figure 2L)** and the Netherlands following the introduction of the hemophilus vaccine.

## *3. Hepatitis B vaccine*

### *3A. Hepatitis B vaccine: South Island, New Zealand*

The incidence of type I diabetes in the 0-19 year old age group has been studied prospectively since 1982 in Christchurch, New Zealand and a rise in type I diabetes was noted to

occur in 1989 (164) after the initiation of an hepatitis B immunization program. The government of New Zealand introduced a massive Hepatitis B vaccination program in 1988 which was extended to include all children under 16 and over 70% of children were vaccinated within a few years following 1988 with almost all of the immunization starting after 6 week of life. The initial vaccine was a human blood derived product but was switched to a recombinant vaccine around 1990. The incidence of type I diabetes in persons 0-19 years old living in Christchurch rose from 11.2 cases/100,000 children/year in the years prior to the immunization program, 1982-1987, to 18.1 cases/100,000 children/year ($p=0.0008$) in the years following the immunization 1989-1991 **(Figure 3A)** .A six year follow up 1989-1994 showed the average incidence was 17.2 cases/100,000 or a 50% rise from prevaccination levels **(Table 3A).** The Measles Mumps Rubella vaccine replaced the measles vaccine in New Zealand in 1990 (personal communication, R. Elliott).

### *3B. Hepatitis B vaccine: North Island, New Zealand*

Researchers have shown that the incidence of IDDM has also risen in the North Island (Auckland) following hepatitis B immunization **(Herald, August 13, 1997).** Dr. Robert Elliott presented data at the International Society for Pediatric and Adolescent Diabetes, September 1998, Zurich that the incidence of IDDM rose following the introduction of the hepatitis B vaccine **(Table 3B, Figure 3B, 3C).** The problem with the North Island data is that the population is more transient, and the population has risen in the Auckland area, making the data less accurate than the South Island (personal communication R. Elliott). However, the trend is the same as with the South Island.

### *3C. Hepatitis B vaccine: US*

A US government funded study (165) was conducted to confirm the findings in New Zealand. The preliminary data found an increased risk of type 1 diabetes when the hepatitis B vaccine was given starting after two months. The odds ratio was 1.9 with an average follow up of 22 months which was similar to the findings in New Zealand **(Figure 3D).**

### *3D. Hepatitis B vaccine: Italy*

A cohort analysis was performed to measure the incidence of type 1 diabetes in hepatitis B vaccinated and unvaccinated cohorts from Central Italy. Mandatory hepatitis B immunization was implemented in Italy in 1991 and required all children to receive the hepatitis B vaccine when they turned 3 months old or 12 years of age. No catch-up program was implemented for children between these time frames. All cases of Type 1 diabetes occurring in children under 15 years of age have been collected in a prospective diabetes registry in Rome and the Lazio Region of Italy since 1989 (EURODIAB). Children were given recombinant hepatitis B vaccine. Separate cohort analysis was performed on children who were immunized starting between 2-3 months of life and 12 years of age.

The cumulative incidence of type 1 diabetes in the vaccinated and unvaccinated group under 6 was 51 and 41 cases 100,000, respectively, with a relative risk of 1.24 (p=0.2). In the cohort of children 12 years of age (vaccinated and unvaccinated) and followed through age 14, the cumulative incidence of Type 1 diabetes was 23 and 10.3 cases/100,000 respectively, with a relative risk of 2.22 (p=0.036). The combined relative risk in this study was 1.4 (p=0.039). The risks appeared higher with the higher dose of vaccine.

### *4. BCG Vaccine*

#### *4A. BCG vaccine: European ecological studies*

An extensive study of the incidence of IDDM in Western Europe (39) shows that those countries giving the BCG vaccine starting after 2 months of age, most commonly at school age, have an increased incidence of IDDM. This ecological study indicates BCG immunization starting after two months is associated with a relative risk of 1.74 **(Figure 4A).**

#### *4B. BCG vaccine: Canada*

Data from a case control study from Quebec (166) confirmed ecological data that the BCG vaccine when given starting after 2 months of life is associated with an increased risk of IDDM. The authors (167) found 14 of 249 diabetics had received BCG immunization after 1 year of life versus 12 of 431 controls, odds ratio 2, relative risk 1.5 (95% confidence, 1.03, 2.17) **(Figure 4D).**

#### *4C. BCG vaccine: Denmark*

The BCG vaccine was routinely given to children in Denmark starting at school age, 7 years old. In 1989 the first county in Denmark stopped BCG immunization. BCG was removed form the list of government funded vaccines in 1990 and other counties stopped BCG immunization between 1990-1992 (personal communization, Troels Boch). Following this discontinuation of the BCG vaccine the incidence of IDDM declined 9% per year during the 6 year interval from 1989 to 1994 (P= 0.02) (150). This amounts to a 38% decline in the incidence of IDDM. A recent publication on the trends of IDDM in Europe (150) shows Denmark, and only Denmark out of 29 countries, had a statistically significant drop in the incidence of IDDM during the interval 1989-1994.

Data on the incidence of IDDM in 4 counties in Denmark in the years 1989-1993 has been published (168). In the years 1989-1993 the average incidence was 17.4 cases of IDDM/100,000 with a total of 201 cases of IDDM identified. The data on the incidence of IDDM for the same 4 counties but including cases identified in 1994 indicated an average incidence of

16 cases/100,000 with a total of 221 cases of IDDM identified (150). This indicates that 20 new cases of IDDM occurred in 1994. The incidence of IDDM for the year 1994 can be calculated to be 8.8 cases/100,000 **(Table 4A; Figure 4A, 4B, 4C)**.

The incidence of IDDM declined 38% during the time frame 1989-1993 based on a hypothesis of a linear trend (150). According to the publication (150) In this time frame the risk ratio per year was .91, indicating a 9% decline per year for 5 years (P=0.02). This results in a cumulative decline of 38%, ($.91^5$=.62 or 62%). This indicates the relative risk associated with BCG vaccination is 1.61 (1/.62) which is remarkably close to a published estimated relative risk of 1.71 based on ecological data (39) and 1.5 based on a Canadian case control study.

The decline in the incidence of IDDM in Denmark following the discontinuation of the BCG vaccine is even more impressive when comparing the incidence of IDDM in Denmark to Iceland. People of Iceland are of Scandinavian origin like the people of Denmark and share many genes. Iceland was even a colony of Denmark from 1380 to 1944. In 1989 the incidence of IDDM in Iceland was similar to countries giving similar vaccines and was notably lower than other Scandinavian countries. The incidence of IDDM in Denmark was considerably higher than that of Iceland, but similar to that of other countries with a similar immunization schedule (39). After the discontinuation of the BCG vaccine the incidence of IDDM in Denmark declined to about 9 cases/100,000 **(Table 4A, Figure 4C)** and was actually less than the rate of Iceland. This is strong support for a causal relationship between the BCG vaccine and IDDM.

### *4D. Timing of BCG immunization*

Differences in the incidence of IDDM associated with differences in timing of immunization provide support for a causal relationship between vaccines and adverse events. Immunization with BCG starting at birth is associated with a decreased risk of IDDM **(Figure 4E)** while immunization starting at school age is associated with an increased risk of IDDM **(Figure 4A, 4D)** (39). The data supporting this includes birth cohort data from Sweden and European ecological data (39).

## *5. Measles, Mumps, Rubella vaccine*

### *5A. Measles, Mumps, Rubella vaccine: Finland*

Rises in the incidence of IDDM occurred in Finland following a massive immunization programs with the live trivalent viral vaccine to protect against measles, mumps and rubella (MMR) . The vaccine regiment in Finland was altered by replacing the measles vaccine with the measles, mumps, rubella, vaccine at age 14 month and 6 years in 1982 (151). Following the introduction of the live virus MMR there was a rapid rise in incidence of IDDM in children aged 1-4 in 1983. This was followed by a lower incidence of IDDM in children age 1-4 in 1984 and 1985. In 1986 and years following this the incidence of IDDM remained consistently high

**(Figure 5A)**. Analysis of incidence data using averages of 3 year periods shows the incidence of IDDM was stable at a yearly rate of about 23 cases/100,000 from 1977-1985. The rate rose to 29 cases/100,000 starting in 1986, an relative risk of 1.29, and remained elevated. The delay in the rise of IDDM is consistent with a delay between exposure and the development of IDDM of about 2-4 years as discussed above. The initial spike of IDDM in 1983 may be explained by a coincidence, a shorting of the honeymoon period second to release of interferons causing insulin resistance, or a subgroup of patients developing a fulminating infection from the vaccine virus causing rapid destruction of islet cells.

The MMR vaccine was also given to children 6 years of age in Finland (151). A large rise in the incidence of IDDM occurred in children age 6 (156) which coincided with the introduction of the MMR vaccine and the incidence of IDDM in the 5-9 age group rose in the 1982-1984 period following the introduction of the vaccine, (figure 1 (169) ). The incidence was about 32 cases/100,000 in children in the years 1976-1981. This rate rose and remained stable at about 39 cases/100,000 in the years from 1982-1993 **(Figure 6C).** This represents a relative risk of 1.22. This rise can be attributable to both the MMR vaccine and the new more potent pertussis vaccine.

A birth cohort study was performed by Hyoty et al. in Finland looking at the affect of the measles mumps rubella vaccine on the incidence of IDDM in Finland (151). The study was flawed as discussed below **(Section IX, 2B ).** In children immunized at age 6 and followed for the development of IDDM between age 7-9, the cumulative incidence in unimmunized birth cohorts 1970-1975 is 108 cases/100,000 while the incidence in the immunized birth cohorts 1976-1981 is 115.5 cases/100,000. The relative risk is 1.07 in this age group. By contrast in children immunized at age 1 and followed for development of IDDM through age 4, the incidence of IDDM in the unimmunized birth cohorts was 95.4 cases/100,000 and the incidence in the immunized birth cohorts 1981-1986 was 114.7. The relative risk is 1.20. **(Figure 5C)** . The later is similar to the rise in IDDM that was seen in the age groups 1-4 and 5-9 described above, 1.29 and 1.22 respectively . However, the relative risk described in the cohort study for age 7-9 was only 1.07.

The reason Hyoty's calculated risk of the MMR vaccine is lower than the ecological analysis can be explained in part by the shorter follow up. Hyoty did not followed the children for the full 4 years after immunization and thus likely missed a large number of cases of vaccine induced IDDM. For example in children immunized at age 6, Hyoty did not start measuring the cumulative incidence of IDDM until the children reached age 7. However, Hyoty indicates he could not have followed all the children through age 9. For example the children born in December of 1981 were followed through the end of 1990 for the development of IDDM. Therefore they would have barely reached age 9 by the end of the study, and they would not have been followed through age 9, only until age 9. In a like manor he could not have followed children immunized at 18 months through age 4. A second problem is that there was a catch-up immunization program and some of the children in the unimmunized cohort received the MMR

vaccine. A third problem with his analysis is the confounding effect of the pertussis vaccine as described below.

### *5C. Measles, Mumps, Rubella vaccine: United Kingdom*

The measles vaccine was replaced by the MMR in the UK starting in 1988 and given to children around 18 month of age. The average incidence of IDDM in the 4 years surrounding the initiation of the MMR vaccine was approximately 10 cases/ 100,000/year however within 2 years of the introduction of the MMR vaccine the incidence rose 12.2 cases/100,000/year **(Table 5A, Figure 5B)**.

### *5D. Measles, Mumps, Rubella vaccine: New Zealand*

The MMR vaccine replaced the measles vaccine in New Zealand starting in 1990. This followed the introduction hepatitis B vaccine which occurred in 1988. A large rise of IDDM followed the introduction of the hepatitis B vaccine and the MMR vaccines **(Tables 3A, 3B, Figure 3A, 3B).**

### *5E. Measles, Mumps, Rubella vaccine: antibody studies*

Bodansky et al. (18) studied the development of anti-islet cell antibodies in 239 children who were 10 years old when they received live rubella vaccine. They found 2.9% of girls had antibodies before immunization and 4.2% had antibodies 6 weeks after immunization.

### *5F. Measles, Mumps, Rubella vaccine: EURODIAB multicenter study*

A multicenter case control study (105) was performed to evaluate the effect of vaccines on IDDM. The data indicated the measles, mumps, and rubella vaccines are associated with odds ratios of 1.02, 1, 1.18 respectively. The same case control study using a multivariate analysis to compensate for confounding variables found that the vaccines were associated with odds ratios of 1.1, 1.03, 1.27 respectively **(Table 30A, Figure 3C).**

### 5G. *Measles, Mumps, Rubella vaccine*: Sweden

A case control study was performed in Sweden to asses the effect of vaccines on IDDM. The study attempted to include all cases of IDDM occurring between September 1985 and August 1986. Two controls were matched to each case and matching was based on age, sex and county. A total of 338 cases and 528 controls were eventually included in the study. The study

found the rubella vaccine was associated with an odds ratio of 1.24, similar to what was found in Finland and a multicenter ecological study. The mumps vaccine was associated with an odds ratio of 1.75 and the measles vaccine was associated with an odds ratio of .74. The study was too small to reach statistical significance with any of the three vaccines alone only the use of measles, mumps rubella vaccine or measles vaccine was associated with an odds ratio of .69.

***6. Pertussis vaccine***

***6A. Pertussis vaccine: Finland***

The pertussis vaccine has been given in Finland according to a 4 dose regiment starting at 3 months of age with the last booster dose given before 24 months (170). The incidence of diabetes was stable in the 1-4 year old age group in Finland from 1966-1977 at around 15 cases/100,000 per year. In 1976 the pertussis vaccine was made more antigenic by the addition of a second strain of bacteria (171). This change was followed by an 53% rise in IDDM as the incidence rose to 23 cases/100,000 and remained stable from 1978-1986 (156) **(Figure 6A).** The incidence of IDDM also rose in the age group 5-9 but the maximum effect of this rise was delayed until those born after 1976 reached age 5. The incidence of IDDM varied from 26- 33 cases/100,000 between the years 1970-1981 but stabilized at approximately 39 cases /100,000 from 1982-1993 **(Figure 6C)**. The rise in the 5-9 year old population was also confounded by the introduction of the MMR vaccine in this age group starting in 1982.

A birth cohort study was performed by Hyoty et al. in Finland looking at the affect of the measles mumps rubella vaccine on the incidence of IDDM in Finland (151). While unplanned by Hyoty, he measured the cumulative incidence of IDDM in the birth cohorts born after 1976 which received the new more potent pertussis vaccine and in birth cohorts born before this. He directly compared the cumulative incidence of IDDM in children born between 1973-1975 to children born between 1976-1980. He found the cumulative incidence in children aged 0-4 in the two cohorts to be 82 cases/100,000 and 102.9 cases/100,000 respectively ($P<0.05$), relative risk 1.25 **(Figure 6B)**.

The study was flawed as discussed below **(Section IX, 2B ).** The reason the relative risk is lower in Hyoty's cohort analysis than in the ecological analysis can be explained in part by the shorter follow up. Hyoty did not followed the children for the full 4 years after immunization and thus likely missed a large number of cases of vaccine induced IDDM. For example the children born in December of 1975 were followed through the end of 1979 for the development of IDDM. Therefore they would have barely reached age 4 by the end of the study, and they would not have been followed through age 4, only until age 4. A second problem is that children born in 1974 and 1975 would have been offered the routine 2 year booster dose of the new more potent pertussis vaccine in 1976 or afterwards. A third problem with his analysis is the confounding effect of the MMR vaccine as described above.

***6B. Pertussis vaccine: United Kingdom***

During the period of 1975 to 1979 immunization with the pertussis vaccine dropped in several countries including the United Kingdom where acceptance rate fell from 75% in 1974 to 30% in 1978 (172). Data from Yorkshire (173) showed a drop in the incidence of IDDM in children age 0-4 which reached a trough in 1982, 3 years after the tough in immunization rates with the pertussis vaccine. The incidence of IDDM went from 9.5 cases of IDDM/100,000 in 1979 to approximately 6.5 in 1982 and back to 9.8 in 1985. This is consistent with a relative risk of 1.46 **(Figure 6E)** . The rise in IDDM correlated with the rise in immunization rate. Between 1979 and 1986 the immunization rate went up 75% and the incidence of IDDM rose 85% from 1982-1989.

### *6C. Pertussis vaccine: Sweden*

The effect of the DTP vaccine on IDDM was studied in Sweden (174). The study involved comparing the cumulative incidence of IDDM in birth cohorts that received a DTP vaccine lacking an aluminum adjuvant (1977 and 1978 birth cohorts) to birth cohorts receiving a DT vaccine containing an aluminum adjuvant (birth cohorts 1980 and 1981). Both groups appeared to have a similar rate of IDDM **(Figure 6D)**. The analysis was flawed because the MMR vaccine was started at about the same time that the pertussis vaccine was discontinued in Sweden. The 1977 and 1978 birth cohorts which received the pertussis vaccine did not receive the MMR vaccine at 18 months. The 1980 and 1981 birth cohorts which did not receive the pertussis vaccines but did receive the MMR vaccine. Thus the results indicate the pertussis vaccine had an effect similar to the addition of the MMR vaccine, the latter is consistently associates with an relative risk of approximately 1.2.

### *6D. Pertussis vaccine: Italy*

The Italians have low uptake of pertussis immunization and generally have lower rates of IDDM than comparable countries (39).

### *7. Diphtheria Tetanus vaccine*

A multicenter case control study (105) was performed to evaluate the effect of vaccines on IDDM. Case control data indicates the tetanus vaccine is associated with a relative risk of 1.2 and the diphtheria vaccine is associated with a relative risk of 1.09. The combined relative risk of the DT vaccine is 1.31. The same case control study using a multivariate analysis to compensate for confounding variables found that the tetanus vaccine was associated with a relative risk of 1.56 And the diphtheria vaccine with a relative risk of 1.27 and a combined risk of 1.98. This data is consistent with data on Swedish military recruits which receive the DT vaccine and have a relative risk of 2 compared to women who were not in the military (175).

*8.Polio vaccine*

A multicenter case control study (105) was performed to evaluate the effect of vaccines on IDDM. The study estimated the polio vaccine associated with a odds ratio of 1.03 (105). A case control study from Sweden estimated the polio vaccine to be associated with an odds ratio of 1.03 (176). These analysis are likely to underestimate the effect of the polio vaccine on the incidence of IDDM because case control studies greatly underestimate the association when there is very high utilization of the vaccine.

*9. Smallpox vaccine*

*9A Smallpox vaccine: Sweden*

Swedish law until early 1976 required immunization with smallpox vaccine prior to the age of 5 and the vaccine was administered primarily at 2 months or 9 months of age (177). Detailed records on the acceptance rates with the smallpox vaccine in the birth cohorts are not available. Swedish public health officials have indicated that the smallpox vaccine was being increasingly withheld in anticipation of the discontinuation of the law, as it became apparent to physicians that the risk of children developing adverse responses from immunization exceeded the risk of being infected with smallpox. A decline in the acceptance rate of the smallpox vaccine in Sweden is supported by World Health Organization records, the number of doses of smallpox vaccine administered in 1972, 1973, and 1974 were 948,000, 898,000, and 807,000 respectively (WHO Health Statistics Annual). Data from the Netherlands showed this trend clearly. In the Netherlands the smallpox vaccine was given around 9 month of age and was mandatory by age 1 before the law was repealed on November 28, 1975. The acceptance rates by age 1 in the Dutch birth cohorts of 1970-1975 were 88%, 87%, 82%, 66%, 47%, and 9% respectively.

The cumulative incidence of IDDM in children followed from ages 4-15 has been performed on different Swedish birth cohorts about the time of the discontinuation of the Smallpox vaccine. The analysis of the effect of the smallpox vaccine is confounded by the discontinuation of the newborn BCG immunization in 1975 (39,178). **Table 9A** shows the cumulative incidence in the different birth cohorts. The 1973 birth cohort is expected to have a higher immunization rate with smallpox vaccine than the 1974 birth cohort. Also the 1975 birth cohort is expected to have a higher smallpox immunization rate than the 1976 birth cohort. The effect of the smallpox vaccine on IDDM would be greater than the sum of the differences between 1973 vs 1974 cohorts and the 1975 vs 1976 cohorts. The attributable effect of the smallpox vaccine is thus 33 cases/100,000 or an relative risk of 1.10.

*9B. Timing of smallpox immunization*

Differences in the incidence of IDDM associated with differences in timing of immunization provide support for a causal relationship between vaccines and adverse events.

Changes in smallpox immunization practices correlate with large swings in the cumulative incidence of IDDM in the Netherlands (179) A low cumulative incidence of IDDM was reported in Dutch males born in 1962 (180) compared to males born in previous or later years. The decline in incidence of IDDM correlates with years when the smallpox vaccine was given more frequently and expected to be given earlier.

Epidemiology data shows that in the cumulative incidence of IDDM up to the age of 18 differed significantly in Dutch male birth cohorts (180). There were two significant drops in the incidence of IDDM, one was centered around 1962 when the cumulative incidence dropped to 1.1 per 1000 ($P<.05$), and the other was centered around 1966 when the cumulative incidence dropped to 1.71 per 1000. The drops are in contrast to a cumulative incidence of IDDM outside of these troughs of about 1.98 per 1000 **(Figure 9A)**. The drops in 1962 and 1966 both occurred during smallpox epidemics in Europe and can be explained by immunization of newborn infants in these periods with smallpox vaccine.

Western Europe had major epidemics of smallpox centered around the years 1962 and 1966. The epidemic in 1962 actually started in 1961 continuing into 1963 and included 158 cases from 7 western European countries (181). The 1966 epidemic included 72 cases and was limited to the United Kingdom. There was a strong emphasis placed on vaccination during the smallpox epidemic of 1961-1963 as demonstrated by World Health Organization statistics showing 23.5 million Europeans were vaccinated with the smallpox vaccine in 1962 compared to an norm of about 11 million in non epidemic years (182). Changes in smallpox vaccine acceptance were detected around 1962 and 1966 in the Netherlands (183).

It was customary at the time for physicians practicing in areas with a low incidence of smallpox to wait until the patient was several months old before administering the smallpox vaccine, however in areas with high incidence of smallpox, like third world countries, smallpox vaccine was often given at birth (184) (185). The common practice in the Netherlands in the 1960s was to immunize children with the smallpox vaccine starting at 2 months of age in normal, non epidemic conditions (186). Given the fact that the vaccine literature recommends immunization earlier than usual in times of epidemics, it would have been expected that a number of physicians would have given the vaccine several weeks earlier, as in 4 weeks of age or at birth. The resulting switch in immunization can explain the drop in the incidence of IDDM in the cohorts born during smallpox epidemics. The approximately 50% decrease in the incidence of IDDM by age 18 which occurred could be expected if the smallpox vaccine were given on average 3 weeks earlier (39).

### *10. Military vaccines*

American troops are heavily immunized and we attempted to determine if immunization of military personnel is associated with an increased risk of IDDM.

Medline was searched to locate publications on the incidence of IDDM in civilians aged 18-35 and people in the military in western industrialized nations. Key words used in the Medline search were diabetes, insulin and incidence. References of papers found were used to find additional texts. We prospectively planned to include only papers on Caucasian populations from Western Europe countries, United States, Canada, Australia, and New Zealand because we felt the standards of living and medical care of the Caucasian populations in these countries were similar and our previous studies had revealed an effect in children living in these countries. We limited our search to papers containing incidence data primarily from 1975 to present and containing at least 100 cases of IDDM in the study range.

After we identified countries with data meeting the criteria mentioned above , Internet Search engines including Yahoo and Hotboot were used to determine the status of military conscription in these countries. The name of the country, military, and conscript, were used as key words for the internet search. In the case of Belgium we contacted the library of the military academy by e-mail to find out when the draft was ended.

The mean incidence of IDDM in the control group was determined by a weighted numerical average, using the sum of all the cases of IDDM and the years of follow up from all centers. The incidence of IDDM at any given sex and age group was published for each center . All centers except Sweden published the number of cases of IDDM for each sex and age group. For Sweden the total number of cases for males and females was published for the ages 15-35 and the number of patient year follow up was published. Based on this information and the incidence of IDDM for each age and sex group , an estimate of the number of cases of IDDM was calculated. To be conservative with the Swedish data we used a patient year follow-up size, 1 million, in each group that was in the minimum of the range we expected for each group.

Relative risks and other calculations were made using Epi 6 software (WHO). A 2x2 table was used and included the total number of cases of IDDM and numerator for the control group and the US navy. Uncorrected chi square test was used. Taylor series 95% confidence limits were used. Figures on the relative risk were rounded to the nearest tenth

The computerized search revealed published papers on the incidence of IDDM from the US navy and several Western European countries however we did not find studies from Australia, New Zealand, Canada and several Western European Countries. The incidence of IDDM for adults age 15-35 was available **(Table 20)** for Sweden (175), Italy (187) (188), Belgium (189), Spain (190), Norway (191) (192). All of these countries had laws drafting men but not women. The incidence of IDDM was also published on white men and women who joined the US navy (193). No other studies were found that met the entry criteria.

The data indicates that in the countries where men are drafted but not women the incidence of IDDM is greater in men than women. In those 20 or older the relative risk is 1.68 (1.53 - 1.84) . By contrast in the US military personnel the risk of IDDM is slightly lower in

men then women, relative risk 0.8 (0.64-0.97). In these same countries the relative risk of males/females for children 0-14 is about 1.1.

The risk of IDDM is higher in the US military men than conscripted European men age 20-35 relative risk 1.6 (1.45-1.73), but the relative risk is even higher in US Navy women compared to conscripted women 3.4 (2.7-4.26). The incidence of IDDM in young US military personnel, age 17 to 19 is initially in par with the European populations and US civilians (161) . In male US navy personnel the incidence of IDDM increases gradually over comparable conscripts from European countries with time, relative risk from 1.3 (1.17-1.51) at age 20-24 to 2.5 times (2.01-3.03) at age 30-34. A rise in the relative risk is also seen in US navy women compared to controls, the relative risk rises from 3.0 (2.26-4.07) at age 20-24 to 5.6 (2.9-10.85) at age 30-34. The calculated cumulative increased risk of IDDM in white US military women versus nonconscripted European women from age 20 through 34 is 328 cases/100,000.

There are several findings in this analysis which support an association between vaccination and IDDM. In countries where men, but not women are drafted and are exposed to military immunization, the men have about 1.7 times (1.53-1.84) the risk of developing IDDM as the women. By contrast in the US navy where men and women are both expected to receive military vaccines the incidence of IDDM is less common in men, relative risk 0.8 (0.64-0.97). IDDM is more common in the highly immunized US military men than the less immunized conscripted European men 1.6 (1.45-1.73). However, the risk of IDDM is even more pronounced in US navy women as compared to nonconsripted European women 3.4 (2.7-4.26). The difference in IDDM in the US navy men compared to conscripted men in Europe can be explained by the more extensive use of vaccines in the US military. Sweden's military, for example, during the time frame studied routinely gave the troops the diphtheria -tetanus vaccine but few others (personal communication Herald Heijbel, Infectious disease/vaccine safety expert, Swedish Public Health Department). The US by contrast typically give military personnel many more vaccines.

The incidence of IDDM in the US navy increases with age and years of exposure, further supporting an association between vaccination and IDDM. The incidence of IDDM declines with time in the nonconscripted European women from 10.6 cases/100,000 in the 15-19 age group to 5.9 cases/100,000 in the 30-34 age group, relative risk .56 (0.44-0.72) . By contrast in the heavily immunized navy women the incidence of IDDM increases from 12.6 cases/100,000 in the 17-19 age group to 33.2 cases/100,000 in the 30-34 age group, relative risk 2.63 (1.04-6.69) . A similar though less pronounced effect is seen in men. The in the incidence of IDDM in conscripted European men was fairly constant from 13.5 cases/100,000 in the 15-19 age group to 13.2 in the 30-34 age group, relative risk .97 (.82-1.16). By contrast the incidence of IDDM in the US navy men increases from 12.5 cases/100,000 in the 17-19 age group to 32.4 cases/100,00 in the 30-34 age group, relative risk 2.59 (2.07-3.24). In the US navy men the incidence of IDDM increases gradually over comparable conscripts from European countries with time, relative risk from 1.3 (1.17-1.51) at age 20-24 to 2.5 times (2.01-3.03) at age 30-34 . A rise in the relative risk is also seen in US navy women compared to controls, the relative risk

rises from 3.0 (2.26-4.07) at age 20-24 to 5.6 (2.9-10.85). The rise in the women is about as large as in the men but does not reach statistical significance because of the smaller number of women in the navy.

The relative risk of IDDM between men and women in Belgium is particularly interesting. In those 25 or older the relative risk between men and women is about 2.0, similar to many other countries. By contrast the incidence of IDDM in men and women in the 20-24 age group is about the same. This could be explained by the fact that conscription was canceled in Belgium during the study period. A significant number of people in the 20-24 age group may not have served in the military or served a shorten term and thus had less exposure to vaccines. By contrast the older men had been conscripted into the military, received vaccines, and this would explain the increased risk of IDDM in the men compared to women. It is also possible that the incidence of IDDM was similar in men and women between 20-24 because of sampling error or random variation.

The estimation of insulin dependent diabetes in the US navy was made by hospitalization admissions. This system is less accurate and may include cases of type II diabetes however it may have missed case of IDDM that were treated without hospitalization. The authors however do not believe it over estimates the incidence of IDDM. It appears however the estimation is accurate at least in the younger population. The incidence of IDDM in 17-19 year olds is actually less than comparable groups in Europe and to US civilian population (161) suggesting the ascertainment in the navy may actually underestimate the cases of IDDM. A study analyzing all cases of diabetes occurring in people 15-34 in Sweden (25) indicated that at least 92% of all cases of diabetes diagnosed in people under 30 were classified as type -1 , a result that is in agreement with data from Finland. This data strongly supports the author's contention that the cases in the US navy study were type-1 diabetes.

There are other potential causes of IDDM in military personnel such as travel and exposure to infectious agents in foreign lands. While such factors may affect the outcome of a single study, it is very unlikely they would result in all the associations found in many different studies (39,154,167). Furthermore the majority of conscripts in Europe probably do not travel abroad and thus travel would not explain the difference between men and women in Europe.

Norway has the highest incidence of IDDM and the lowest male/female ratio of IDDM in any European country we studied. This can be explained by the criteria for estimating the incidence of IDDM. The authors state they probably included a number of cases of type II diabetes. Another reason is that Norway, was the only country routinely giving BCG vaccine to adolescents or older individuals at time of the study years. However even with this error, the incidence of IDDM in US navy women is twice as high as women in Norway who are 20 or older.

# VII Attributable Risk

## *1. Introduction*

The risk of IDDM caused by a series of different vaccines can be estimated. A person receiving multiple different vaccines which cause IDDM have a combined risk of vaccine induced IDDM equal to the product of the relative risks for each vaccine. The results show vaccines are expected to cause the majority of cases of IDDM in children receiving multiple vaccines.

## *2. Estimates of relative risk*

The cumulative relative risk of vaccine induced IDDM is included in **Table 30B** The relative risks for separate vaccines come from several different sources.

* **BCG vaccine (Section VI, 4):** This vaccine was not included in the calculation of cumulative risk of vaccine induced IDDM because it is not routinely given in the US. Furthermore the data indicates that immunization at birth with the BCG vaccine is associated with a decreased risk of IDDM while immunization starting after two months is associated with an increased risk of IDDM. Ecological data indicates BCG immunization starting after two months is associated with a relative risk of 1.74 (39) which is supported by a case control study which indicates BCG immunization after 2 months is associated with a relative risk of 1.5 (167). Data from the discontinuation of BCG immunization in Denmark indicates the relative risk is 1.6.

* **Hemophilus influenza B vaccine (Section VI, 2)** : A cohort study from Finland showed one and four doses of Hemophilus vaccine (PRP-D) associated with relative risks of 1.10 and 1.17 at 10 years respectively (154). This is consistent with a rise in auto antibodies consistent with IDDM, relative risk of 1.18 (163). A case control study found the hemophilus vaccine associated with a relative risk of 1.16 (105). Ecological data from Finland indicates the PRP-T hemophilus vaccine associated with an relative risk of 1.2

* **Hepatitis B vaccine (Section VI, 3):** An ecological study in New Zealand found hepatitis B immunization starting after 2 months of life associated with an relative risk of 1.6 with 3 years of follow up and a relative risk of 1.54 with 6 years follow up. A cohort study in Italy found the hepatitis B vaccine associated with an relative risk of 1.4 with 3 years or more of follow up. A case control study in the US found the hepatitis B vaccine given starting after 2 months associated with a relative risk of 1.9 with 22 months of follow up.

* **Diphtheria Tetanus vaccine (Section VI, 7):** Case control data indicates the tetanus vaccine is associated with a relative risk of 1.2 and the diphtheria vaccine is associated with a relative risk of 1.09. The combined relative risk of the DT vaccine is 1.31. The same case control study using a multivariate analysis to compensate for confounding variables found that the tetanus vaccine was associated with a relative risk of 1.56 and the diphtheria vaccine with a relative risk of 1.27 with a combined risk of 1.98. This data is consistent with data on Swedish military recruits which receive the DT vaccine and have a relative risk of 2 compared to women who are not in the military and exposed to the diphtheria tetanus vaccine (175).

* **Measles, Mumps, Rubella vaccine (Section VI, 5):** A case control study indicated the measles, mumps, and rubella vaccines are associated with relative risks of 1.02, 1, 1.08 respectively. The same case control study using a multivariate analysis to compensate for confounding variables found that the vaccines were associated with relative risks of 1.1, 1.03, 1.27. A case control study from Sweden found the same vaccine were associated with relative risks of .74, 1.75, 1.24. Ecological data indicates a approximate 10% rise in IDDM in children aged 5-9 in Finland following the introduction of the measles mumps rubella vaccine, relative risk 1.10

* **Pertussis vaccine (Section VI, 6):** Ecological data indicates pertussis vaccine in the UK is associated with a relative risk of 1.4 prior to age 5 . Ecological data in Finland indicates that the improved pertussis vaccine is associated with a relative risk of 1.6 prior to the age of 5. Birth cohort data from Finland showed the pertussis vaccine associated with an relative risk of 1.26 with 4 years of follow up. By contrast a case control study (105) found the pertussis vaccine associated with an relative risk of .89.

* **Polio vaccine (Section VI, 8 ):** Two case control study estimated the polio vaccine associated with a relative risk of 1.03 (105) (176).

* **Combined relative risk of immunization calculations**:

**Table 30B** Provides calculations for cumulative relative risks of vaccine induced IDDM for people receiving several different vaccines.

**3. Conclusion**

The data indicates over 50% of childhood IDDM can be explained by routine childhood immunization. The relative risks of different vaccines on IDDM range from approximately 1 to 2, with the combined use of several different common vaccines associated with a combine relative risk exceeding 3.5. The increased risk of IDDM caused by vaccines is extends for at least 10 years following immunization as demonstrated with the hemophilus vaccine. Booster

vaccines are commonly given every 10 years so the effect of the booster may be multiplicative with the effect of the primary dose.

The magnitude of the risk described above are likely to underestimate the true relative risk of immunization because case control studies greatly under estimate the relative risk of an environmental factor (vaccine) on the incidence of a disease like IDDM when nearly 100% of the population has been exposed. These estimates are in consistent with the elevated risk of IDDM in a highly immunized population, the US navy where the relative risk is reaches 5.6 in women age 30-34. This also explain the 4 fold rise in IDDM in Finland (149) since the 1950s following the introduction of many vaccines. Data is consistent with a low baseline incidence of IDDM in countries prior to immunization and a rapid rise in IDDM in recent years following the introduction of many vaccines.

# IX. Study Failures, Negative Findings, Skeptics

## *1. Introduction*

There are several published papers failing to show an association between vaccines and IDDM. In some cases the failure to show an effect can be explained by an obvious flaw (167). In other cases there appears to be an deliberate omission or misrepresentation of the facts by some one with a under lying agenda to promote vaccines as being safe. Studies failing to show an effect include studies of a small number of children, studies where the end points are antibodies to islet cells instead of diabetes cases, case control studies where the immunization rate is very high, and studies where the basic design was flawed.

It is very easy to manipulate data to argue that there is not statistical association between vaccines and autoimmunity. A certain vaccine may cause less than one in every 1,000 people immunized to develop an specific autoimmune disease such as IDDM. A small sample size will not allow a statistical significance association between the vaccine and the autoimmune disease to be detected. Vaccine promoters including pharmaceutical companies perform a study including a small number of patients and claim the results show no association. These flawed studies however do no detract from the consistent findings in large well designed studies. In conclusion we believe there is clear evidence supporting an association between immunization and IDDM.

In many cases of the papers there is a clear bias not to publish data that may lead people to believe vaccines are causing IDDM or having ill effects. Poutasi, criticizes Classen and the New Zealand Medical Journal for publishing data which links the hepatitis B vaccine to IDDM, "The Ministry has a duty to protect the public health: this includes preventing unnecessary alarm based on unproven hypotheses. Publicizing Classen's hypothesis as fact is both unwarranted and dangerous" (194). "Letters which raise associations such as Classen's can be picked up by the media and cause unnecessary alarm to the public. People who state such associations should publish them as a paper in an established journal, so that there is rigorous peer review of the data and analysis" (195).

Robert Chen and Frank DeStefano of the CDC wrote (196)" We could not agree more that new potential adverse effects of medical interventions should be reported by clinicians as part of their Hippocratic responsibilities and rigorously scrutinized. However, the greater public good would be served if such "signals" were reviewed
through established safety monitoring systems designed specifically for this purpose (e.g., Yellow Card System and the Vaccine Adverse Event Reporting System) and other independent scientific investigations, before claims of possible causality are promoted in medical journals or the mass media."

Vaccine promoters even believe that it is unethical to perform proper safety testing. For example Tuomilehto wrote (197) "Once the efficacy has been confirmed it is therefore neither justified nor ethical to keep control groups of children non-vaccinated for 10 years or longer just as reference for the potential unknown long term consequences of vaccinations to become apparent in vaccinated children." This statement is supported by Jefferson (198).

## *2. Scientific Papers*

### *2A. Hemophilus influenza B vaccine: Finland* (197)

Tuomilehto and others (197) published a study pertaining to the effect of the Hemophilus vaccine on IDDM . They concluded that the hemophilus vaccine was unlikely to cause IDDM. However their analysis was severely flawed (154). The study involved groups receiving 4 doses, 1 dose and 0 doses of hemophilus vaccine. The cumulative incidence of IDDM/100,000 in the 3 groups were 261, 237, 207 at 7 years and 398, 376, 340 at 10 years of age respectively. Tuomilehto's analysis was not rational and his conclusion is not supported by the data. Tuomilehto compared groups receiving 4 doses to 1 dose and groups receiving 1 dose to 0 doses. This analysis minimizes the difference and misleads the reader. His calculations of relative risk are misleadingly low. Most objective researchers would compare the group receiving 4 doses to the group receiving 0 doses. Alternatively they would compare the combined vaccinated groups to the group receiving 0 doses. Both reach statistical significance. The cumulative difference in cases IDDM/100,000 between those receiving 4 doses and those receiving 0 doses is 54 cases (P=0.013) at 7 years and 58 cases at 10 years (P=0.029) using a single tail Fisher test. The relative risk equals 1.26 at 7 years. The cumulative difference between those receiving 4 or 1 doses and those receiving 0 doses is 42 cases (P=0.016) at 7 years and 47 cases at 10 years (P=0.028).

### *2B. Measles Mumps Rubella vaccine : Finland* (151)

The Finnish Public Health Service also studied the effect of the Measles Mumps Rubella vaccine on the development of IDDM (151). Their analysis found an rise in the incidence of IDDM in children under 5 who received a MMR vaccine between age 1 and 2 but only a smaller rise in the incidence of IDDM in children immunized at 6 years of age. The authors concluded that the rise in the incidence of diabetes in Finland plateaued after the introduction of the MMR vaccine and that there was a lack of a cohort effect.

The analysis was flawed (167). The MMR vaccine was given to children 6 years of age in Finland however the authors only studied a cohort effect in children 7 and older (151), thus potentially missing the rise in the incidence of IDDM in 6 year olds who received the vaccine. Another reason why Hyoty's calculation resulted in a low relative risk of the MMR vaccine in the children age 7-9 can be explained in part by the shorter follow up time in the study by Hyoty et al. Hyoty did not followed the children for the full 4 years after immunization and thus likely

missed a large number of cases of vaccine induced IDDM. Conflicting statements in Hyoty's paper indicate they could not have followed all the children through age 9. For example the children born in December of 1981 were followed through the end of 1990 for the development of diabetes. Therefore they would have barely reached age 9 by the end of the study, and they would not have been followed through age 9 only until age 9. Since children were recommended to receive the MMR vaccine some time at age 6 and since they were likely to be followed only until reaching age 9, they could have only been followed for the development of IDDM for two years after receiving the MMR vaccine. In the same fashion the incidence of IDDM in children immunized between age 1 and 2 could not have been followed through age 4 because those born in the end of 1980 were only followed through the end of 1984.

***2C. Measles, Mumps, Rubella vaccine: Sweden***

Bloom et al (176) presented data that the Measles Mumps Rubella (MMR) vaccine may be associated with a protective effect on IDDM, odds ratio 0.69 with confidence interval between 0.48-0.98. The presumed mechanism is that immunization with the live attenuated virus protected children from natural infections with the virulent natural viruses. The did not look specifically at those that were not immunized and did not get infected since these people would be at an increased risk.

The study is extremely difficult to interpret because it did not evaluate the confounding effects of other vaccines. For example 86% of diabetics who were asked to participate entered the study where as only 67% of controls asked to participate did so. The result is that the actual controls that entered the study may not have been well matched for the actual group of diabetics that entered the study. Sweden stopped the BCG (1975), smallpox (1976), pertussis (1979) and started the MMR (1982) vaccines in the 14 years prior to the study and this could have an confounding effect. For example the MMR vaccine was started around the same time the pertussis vaccine was discontinued. The 1980 birth cohort was the first not to receive the pertussis vaccine and the first to receive the MMR vaccine. A child not receiving the MMR vaccine was likely to have received the pertussis vaccine. Furthermore a child not receiving the single measles vaccine would not have received the MMR vaccine. The measles vaccine could appear associated with a decreased risk of IDDM because the alternative was to receive the MMR vaccine which was more diabetogenic.

Lindberg et al. (199) found no rise in autoantibodies associated with autoimmunity to islet cells following the MMR vaccination of 386 Swedish 6 graders, age 12. One major problem with this study is that immunization with the MMR vaccine is associated with possibly 20 cases of IDDM /100,000 immunized and thus one would have to immunize between 5,000 people to see one extra case of IDDM.

***2D. DTP vaccine: Sweden*** (174).

The effect of the DTP vaccine on IDDM was studied in Sweden (174). The study involved comparing the incidence of IDDM in birth cohorts that received a DTP vaccine lacking an aluminum adjuvant (1977 and 1978 birth cohorts) to birth cohorts receiving a DT vaccine containing an aluminum adjuvant (birth cohorts 1980 and 1981). Both groups appeared to have similar rates of IDDM. The analysis was flawed because the MMR vaccine was started at about the same time that the pertussis vaccine was discontinued in Sweden. The 1977 and 1978 birth cohorts received the pertussis vaccine but did not receive the MMR vaccine at age 18 months. The 1980 and 1981 birth cohorts did not receive the pertussis vaccines but did receive the MMR vaccine at age 18 month. Thus the results indicate the pertussis vaccine had an effect similar to the addition of the MMR vaccine, the latter is consistently associates with an relative risk of approximately 1.2. Furthermore based on the study it is not possible to distinguish the effect of the aluminum adjuvant from the pertussis vaccine. Therefore one can not make a conclusion on the effect of the pertussis vaccine on IDDM. It is likely that both the aluminum adjuvant and the pertussis vaccine increase the risk of diabetes because both are immune stimulants.

***2E. BCG vaccine: Sweden*** (200)

Dahlquist and Gothefors (200) published Swedish data and concluded that the BCG vaccine does not alter the incidence of IDDM. Their analysis was flawed (178), (39) and reanalysis of the data indicates that immunization at birth was associated with a clinically significant reduction in IDDM. The concern with the Dahlquist and Gothefors' analysis is that it fails to acknowledge that the smallpox vaccine was discontinued in 1976 in Sweden, while the BCG vaccine was discontinued in 1975. The smallpox vaccine was administered in Sweden primarily at 2 months or 9 months of age as compared to the BCG vaccine which was administered at birth. Data from NOD mice and human ecological studies show that vaccines administered starting after 2 months of life increase the incidence of IDDM thus having the opposite effect of administering vaccines at birth (39). The Swedish data needs to be analyzed in a way to compensate for the confounding effect of the smallpox vaccine.

Swedish law until early 1976 required immunization with smallpox vaccine prior to the age of 5. Unfortunately good records on the acceptance rates in the birth cohorts are not available. Swedish public health officials have indicated that the smallpox vaccine was being increasingly withheld in anticipation of the discontinuation of the law, as it became apparent to physicians that the risk of children developing adverse responses from immunization exceeded the risk of being infected with smallpox. Data from the Netherlands showed this trend clearly. In the Netherlands the smallpox vaccine was given around 9 month of age and was mandatory by age 1 before the law was repealed on November 28, 1975. The acceptance rates by age 1 in the Dutch birth cohorts of 1970-1975 were 88%, 87%, 82%, 66%, 47%, and 9% respectively.

**Table 4B** analyzes the differences between the birth cohorts which received BCG, 1973-1974, and those that didn't, 1976-1977. Dahlquist and Gothefors' analysis which ignores the effect of the smallpox vaccine is listed as assumption A. Three additional assumptions were included which refrain from comparing the 1973 to the 1977 cohort because the variation in

acceptance rate of the smallpox vaccine between these cohorts is the greatest. The administration of BCG at birth is associated with a drop in the cumulative incidence of diabetes by 32-49 cases of diabetes/100,000 individuals. The most appropriate way to compensate for the confounding effect of the smallpox vaccine would be to compare the 1974 and 1976 cohorts, which show a difference of 48.64 cases/100,000. The cumulative effect of administering a BCG vaccine at birth according to this ecological data is 52.8 cases/100,000 (39) and thus consistent with the data from Sweden.

### *2F. BCG vaccine: Canada* (166)

A paper from Montreal (166) was published on an association between the BCG vaccine and the incidence of IDDM in Quebec. The Montreal paper contains two separate case control studies, series A and B. Series B analyzed cases of IDDM in 0-18 year olds occurring between 1982 and 1986. Series A pertains to a subpopulation of children 7 or older. The authors concluded that their was no effect of the BCG vaccine on the development of IDDM. The analysis was flawed however because it did not consider the effect of timing of the first dose of BCG vaccine on the development of IDDM. Sufficient data was not available to determine how many children immunized in the first year of life were actually immunized in the first month of life. However analysis of cases and control immunized starting after 1 year of life with the BCG vaccine indicates the vaccine is associated with an increased risk of IDDM.

Series B contained 249 cases of IDDM and 431 prospectively collected matched controls age 0 through 18. The authors found 14 of 249 diabetics had received BCG immunization after 1 year of life versus 12 of 431 controls, odds ratio 2. This is consistent with ecological data from Europe (167). Data from Series A that was published (166) was incomplete and not easily analyzable.

### *2G. Hepatitis B vaccine: Poutasi* (195) (194)

Karen Poutasi, the Minister of Health in New Zealand, published two letters trying to refute an association between the hepatitis B vaccine and a rise in the incidence of IDDM in the South Island of New Zealand (Christchurch). Her reasons for believing that the hepatitis B vaccine do not cause IDDM include the following.

Her first reason was "The Auckland registry did not exhibit any epidernic increase after December 1989 when hepatitis immunisation was recommended at age 6 weeks (R Elliott, personal communication)." (194). She states "Classen fails to explain why the Auckland diabetes registry did not show any increase following the introduction of the Hepatitis B vaccine." The truth however is that the incidence of IDDM rose substantially in Auckland following the introduction of the hepatitis B vaccine **(Herald, August 13, 1997).** Data was presented by Dr. Robert Elliott at the International Society for Pediatric and Adolescent Diabetes, September 1998, Zurich meetings confirms this **(Table 3B)** . The problem with the

North Island (Auckland) data is that the population is more transient, and the population has risen in the Auckland area, making the data less accurate than the South Island. However the trend is the same in both islands.

Her second reason was "The Christchurch registry does show an increase in IDDM incidence during 1989-91, and Classen suggests that this is caused by hepatitis B immunisation. Analysis of the registry data does not support his hypothesis (R Scott, personal communication)." The analysis she refers to is one performed by Dr. Willis and Scott discussed below which is clearly flawed.

### *2H. Hepatitis B vaccine: Willis* (201)

Jinny Willis and Scott (201) question the published association (164) between the hepatitis b vaccine and the development of IDDM in New Zealand. They analyzed the incidence of IDDM in children born before February 1988 to children born after this time. The analysis was flawed for two reasons. First it assumed those born prior to 1988 did not receive hepatitis B vaccine. In fact there was a massive catch-up program in New Zealand with the hepatitis B vaccine originally given to all preschool children (202) but was soon expanded so that all the children under the age of 16 received the hepatitis B vaccine, not just those born after 1988. The acceptance rates were estimated to be above 70% (Personal communications, Dr. Harry Nicholls, Senior Advisor for Communicable Diseases, Ministry of Health, Wellington, NZ). Thus children born in the 1970s and early 1980s received the hepatitis B vaccine.

Second the incidence of IDDM differs depending on the age of the child in most countries including New Zealand, with fewer cases of IDDM occurring in ages 1-5 versus 10-14 (203) . Willis' analysis only proves that the incidence of IDDM is higher in older children (those born before 1988) than the very young children (those born after 1988).

### *2I. Hepatitis B vaccine: Petousis-Harris* (204)

Petousis-Harris attempts to discredit an association between the hepatitis B vaccine and the development of IDDM in New Zealand by reciting flawed research by Willis (201). The authors admit in contrast to Poutasi that there was a rise of IDDM following hepatitis B vaccine in the North Island of New Zealand. They say an rise in IDDM was expected. There is thus is a clear contradiction in the New Zealand Public Health Department's statements. First Poutasi denies there is a rise of IDDM in the North Island following the introduction of IDDM. Once they had to admit a rise in IDDM occurred following the hepatitis B vaccine they wrote that it was expected. Clearly the rise was not expected or they would have stated that first (195) (194).

### *2J. EURODIAB multicenter study* (105)

A seven center collaborative study looked for an association between vaccines and the development of IDDM (105). The study involved 900 diabetic children and 2,302 controls. The results are included in **Table 30A.** The data shows the hemophilus vaccine was associated with a Relative Risk of 1.16 which is consistent with the effect of the Hemophilus vaccine on the incidence of IDDM in a cohort study from Finland (154). The diphtheria, tetanus, measles, rubella and polio vaccines were also associated with an increased risk of IDDM though not statistically significant alone. The combined effect of the vaccines was associated with a relative risk of 1.7. The authors erroneously conclude "vaccinations do not exert any major modifying effect on the risk of IDDM". The finding are clearly clinically significant. The authors made the erroneous conclusion based on the fact that their study was too small to achieve statistical significance with clinically significant relative risks. Case control studies generally under estimate the risk of vaccines since vaccines tend to administered with very high uptake.

### *2K. Austria* (205)

Austrian data from the above multicenter case control study (105) was published separately. The analysis from the larger study is analyzed above. The Austrian data involves only 110 patients from the larger multicenter study. The lack of an association between vaccines and IDDM seen in the Austrian data can be explained by the small size of the study and the flawed design. Exposure to vaccines in the Austrian study represented complete immunization while lack of immunization represented those people who did not complete the recommended number of shots for a given vaccine. Data on the hemophilus vaccine from Finland (154) indicates that there is likely to be little difference expected in the incidence of IDDM between those receiving 3 and those receiving 4 doses of the HiB vaccine since the majority of the effect on IDDM occurs with the first shot. Furthermore prediabetics may experience more severe acute adverse events following immunization because of their hyperactive macrophages (42,43) thus they may be less likely to complete immunization than people who do not have a propensity for IDDM. This would give the erroneous interpretation that the vaccine was protective against IDDM using a case control design similar to that used by the Austrians.

### *2L. Vaccines and autoantibodies* (163)

Graves et al (163) published a paper which questioned the ability of the hemophilus and other vaccines to cause IDDM. She employed a case control study and concluded that vaccines don't cause IDDM. Graves relied on a single autoantibody to predict the development of IDDM and it is well known that a single autoantibody has very low specificity for predicting the development of IDDM. She studied only 25 individuals with an autoantibody and 292 controls. Only 5 antibody positive children in Grave's study group developed diabetes. In summary her study was too small, follow up too short, and markers too nonspecific to consistently make the findings seen in Finland (154). However, even with all these limitations Graves' found the hemophilus vaccine associated with an odds ratio of 1.18 (72/62, Graves' Table 1) which was similar to the relative risk of 1.19 (166/140) found the hemophilus vaccinated children by age 5

in Finland (154). Therefore her data actually supported an association between the hemophilus vaccine and IDDM in contrast to what she states (206) .

Graves looked at other vaccines besides the hemophilus vaccine. Most of the vaccines were received by a high percentage of children. It is not possible to study the association between a vaccine and an adverse event like IDDM using a case control study if the vast majority of people in the study population receive the vaccine. For vaccines such as the polio, MMR, and DTP acceptance rates are in excess of 95% so case control studies can not provide useful information for adverse events. There was some variability in hepatitis B immunization however the failure to show an effect can be explained by the study design flaws including the very small number of patients and the use of only a single autoantibody as a marker for IDDM.

### *2K. Vaccines and antibodies in Germany* (207)

A German group performed an almost identical study to that performed by Graves. The case control study involved 29 patients with a single autoantibody associated with the development of IDDM, and 251 controls. Only 4 children actually developed diabetes. Patients were followed for as little as two years after birth. The controls were not matched by age to the cases, and the controls appear to be older, thus likely to have received more vaccines solely because they are older. The study thus contains the same flaws as Grave's study. In summary the study was too small, follow up too short, and markers too nonspecific to consistently make the findings seen in Finland (154).

## 3. Reviews

### *3A. Halsey* (208)

The paper by Halsey pertaining on the Vaccine Safety Workshop is misleading (208). There was no consensus reached by the panel. Panel members, all invited by Halsey, were asked to sign a consensus statement which refuted an association between vaccines and IDDM, the panel refused. Nor was the meeting an objective meeting. Halsey verbally assualted Dr. Classen even before the data was presented and criticized him for discussing the risks of vaccines on television. Halsey's action may be explained by the fact that he was heavily funded by vaccine manufacturers (208) and was actively seeking money from additional manufacturers at the time the meeting was held (personal communications with staff at Johns Hopkins University).

Halsey also misrepresents the data on the hepatitis B vaccine. Immunization with the hepatitis B vaccine starting after 2 months of life was associated with an increased risk of IDDM in New Zealand, relative risk 1.6 (39,164) . The US government performed a small pilot study to determine if the hepatitis B vaccine may modulate diabetes. The preliminary data (165) found hepatitis B immunization starting after 2 months of life was associated with an increased risk of

IDDM, odds ratio 1.9, thus supporting the New Zealand data (164) . Halsey states the US government study indicates early immunization may prevent IDDM.

***3B. Jefferson*** (198,209,210).

Jefferson is an public health official employed by the British military, a large supporter of vaccines. He has published misleading information pertaining to the link between vaccines and IDDM (198,209,210).

Jefferson and Demicheli published a review paper (210) claiming that there is no evidence vaccines cause insulin dependent diabetes (IDDM). Jefferson simply failed to cite animal toxicity studies (138) and epidemiology studies (39) which show immunization starting after 2 months is associated with an increased risk of IDDM. They failed to state that the US government (165) performed a small pilot study to determine if hepatitis B vaccine may modulate IDDM. The US government study found Hepatitis B immunization starting after 2 months of life is associated with an increased risk of IDDM, odds ratio 1.9.

Jefferson (198,209) wrote several misleading letters in the British Medical Journal. In the first letter (198) Jefferson wrote " In May several institutions (including the National Institute of Allergy and Infectious Diseases, Centres for Disease Control, the World Health Organisation, and the UK's Department of Health) sponsored a workshop at the US National Institutes for Health to assess the evidence of a possible causal link. Immunologists, diabetologists, epidemiologists, policy makers, and observers debated the available evidence for two days and concluded that it does not support a causal link between vaccination and the onset of type 1 diabetes." In fact there was no conclusion reached. The sponsor were given ample time to create a possible consensus statement and have the audience vote on it. The sponsors refused.

Jefferson also states "However, the results of a large randomised controlled trial of vaccine against *Haemophilus influenzae* type b carried out in Finland in 1985-7 were reanalysed by Tuomilehto et al and showed no association between the incidence of diabetes mellitus and the addition of another antigen to the schedule, irrespective of timing (unpublished data)." He fails to mention Dr. Classen presented data at the meeting and that analysis shows a statistically significant association between the vaccine and IDDM (154).

In the second letter (209) discussed a Johns Hopkins workshop (208) and NIH workship which "Two independent reviews of available data specific to vaccines were presented by the Cochrane reviewers and the Johns Hopkins Vaccine Safety Institute; neither found an association such as that reported, and both indicated concerns about methodological issues in statistical analysis and the design and conduct of these studies. The conclusion of the workshop, presented in June 1998, was that studies in humans do not indicate an increase in type 1 diabetes attributable to any vaccine or the timing of immunisation. " The truth is there was no consensus

at either the NIH or Johns Hopkins meetings. Panel members at the meeting, were asked to sign a consensus statement refuting an link between vaccines and IDDM but they refused.

*3C. Ellman* (211), (212)

Ellman wrote two misleading letter in the British Medical Journal pertaining to vaccines and IDDM. Ellman wrote (212) "In March 1998 a workshop was convened at the Johns Hopkins School of Public Health to address concerns about the relation between type 1 diabetes and immunisations. The workshop panel was drawn from many disciplines and considered evidence from various sources, including conflicting interpretations of the data from the study reported this week by Karvonen et al. The panel concluded that "selective vaccines are protective against type 1 diabetes in animals but the data in humans are inconclusive and no vaccines have been shown to increase the risk of type 1 diabetes in humans". Bedford and Elliman (211) wrote "The workshop panel (May 1998, Johns Hopkins University) concluded that the analytical methods were incorrect. Furthermore, data were available from Professor Tuomilehto showing that follow up over 10 years showed no difference in the incidence of diabetes between children who had received one dose of vaccine and those who had received four doses. The workshop panel examined evidence from several sources and concluded that "there is no evidence that any vaccines have increased the risk of type 1 diabetes in animals or humans." " Again these statements are false pertaining to the workshop as discussed above. Panel members refused to sign a consensus.

*3D. Hyoty* (169)

Hiltunen et al. also wrote a paper (169) pertaining to vaccines and IDDM, claiming that there is no clear evidence that immunization is associated with insulin dependent diabetes (IDDM). They simply failed to cite animal toxicity studies (138) and epidemiology studies (39) which show immunization starting after 2 months is associated with an increased risk of IDDM. They failed to state that the US government (165) performed a small pilot study to determine if the hepatitis B vaccine may modulate IDDM. The US government study found Hepatitis B immunization starting after 2 months of life associated with an increased risk of IDDM, odds ratio 1.9. Hyoty was also an author of a flawed study looking at the effect of the MMR vaccine on the development of IDDM (167) .

*3E. Thivolet* (213)

Four French authors reviewed flawed research described above but provided little if any new data.

***4. Skeptics and flawed studies***

By the definition of proof, as described above, a causal relationship does not have to be accepted by 100% of the population in order for it to be proved. There are always skeptics who no mater how strong the proof continue to deny an scientific principle. For example many cigarette manufacturers continue to deny tobacco causes health problems. Instead they claim that it is other ill defined behaviors unique to smokers that predispose them to illness. For example smokers may by nature be nervous or may breathe deeper than non smokers and these traits lead to illness, not the tobacco. Such logic while possible is highly unlikely and has not prevented the proving that tobacco has adverse health effects. Many skeptics often have a financial incentive for not accepting proof of a causal event. In some cases the person may work for a company that is being sued as in the case of tobacco industry or the person may be employed as a consultant to the company. Skeptics denying vaccine cause IDDM and other autoimmune disease are in essence denying basic principles of immunology that are well accepted and have been scrutinized through experimentation. Therefore the skeptics do not detract from the proof of a causal relationship between vaccines and IDDM.

# IX. Conclusion

The information above proves that vaccines cause IDDM. The proof includes well accepted mechanism of actions, animal toxicity studies, and epidemiology studies. Biological plausibility and animal toxicity provide strong proof that vaccines cause destruction of pancreatic islet cells. Almost all humans in the world receive many different vaccines. Given the genetic variability of the billions of people immunized it is essentially certain that with many doses of many different vaccines that at least one person would develop IDDM from a vaccine. This is made more credible by the fact that it is known that people are born with a finite number of islet cells which secrete insulin and that these islet cells decline with time (23) . Glucose tolerance tests and simple fasting blood sugars indicate that a number of people are borderline between maintaining satisfactory glucose control and being diabetic. Further destruction of pancreatic islet cells will lead to the development of IDDM in these patients. It is thus very easy to accept that a challenge with a vaccine in some people will lead to the destruction of some islet cells and the development of diabetes in borderline diabetics. It is also easy to accept that since people receive multiple doses of many different vaccines, that the cumulative effect would be the destruction of a significant number of islet cells in some patients.

The support for a causal relationship between vaccines and IDDM is made even stronger by the many different mechanisms **(Section III)** by which vaccines are expected to destroy pancreatic islet cells and cause IDDM. Animal toxicity data **(Section IV)** and in vitro data provide further proof that vaccines cause IDDM in humans. Given the similarity between the mouse and human immune system and the fact that billions of people are immunized it is certain some vaccines will speed the destruction of pancreatic islet cells in some humans as occurs in mice. Epidemiology data proving a causal relationship between vaccines and human autoimmune diseases other than IDDM **(Section V)** is strong proof that vaccines can cause IDDM in some people. Epidemiology data linking natural infections **(Section III)** with autoimmunity especially IDDM provides further proof vaccines cause IDDM.

Many different papers have been written describing how to evaluate epidemiology data to search for proof of a causal relationship between an specific environmental challenge, such as a vaccine, and the development of a specific disease such as IDDM. An paper was written by researchers attempting to determine if a causal relationship exists between the MMR vaccine and autism (4). Several of the points used for proving a causal relationship are summarized in **Table OA** and specific examples are referenced. Data described in **(Section VI)** shows that these criteria are met by vaccines thus proving a causal relationship between vaccines and IDDM. Data from a prospective clinical trial with a HiB vaccine supports a causal relationship. Sharp rises in the incidence of IDDM post immunization were seen in populations where the incidence of IDDM was previous stable for many years before the introduction of a vaccine. Sharp rises or "step ups" post immunization were also seen in the incidence of IDDM in populations where the incidence was rising gradually. A consistent temporal association between vaccines and the rise in IDDM has been demonstrated which ranges from 2-4 years for many vaccines. Congruency

between several different types of studies has been demonstrated. Declines in the incidence of IDDM following discontinuation of vaccines has occurred. Differences in the incidence of IDDM depending on the timing of administration of a vaccine have been demonstrated.

The data indicates that routine vaccines account for over 50% of all cases of IDDM in people receiving many standard immunization schedules **(Section VII).** In an heavily immunized population like the US Navy the incidence of IDDM reaches approximately 5.5 times that in control populations **(Section VII, 10).** The total cost of IDDM in the US is **(Section II, 6)** making vaccine induced IDDM a very expensive disease.

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# XI. Graphs and Tables

## 1. Figure Legends

### Animal Vaccine Figures

**Figure 1A:** Female NOD mice received a series of nine intraperitoneal injections of PBS, using the following protocol: day 1 (.1 ml,), day 3 (.1 ml,), day 10 (.15 ml,), week 4 and every 2 weeks through week 14 (.2 ml) of life. An additional group received only a single injection of whole cell DTP vaccine on week 8 (.2 ml, 1:50). Blood glucose levels were determined at the times indicated and levels over 300 mg/dl were considered positive.

**Figure 1B:** Female NOD mice received a series of nine intraperitoneal injections of vaccines, diluted in PBS, were given to newborn NOD female mice using the following protocol: day 1 (.1 ml, 1:100), day 3 (.1 ml, 1:100), day 10 (.15 ml, 1:100 ml), week 4 and every 2 weeks through week 14 (.2 ml, 1:50) of life. The experimental groups included: anthrax vaccine and the combined diphtheria-tetanus vaccine (A + DT); anthrax and the combined diphtheria-tetanus vaccine with the whole cell DTP vaccine substituted for the diphtheria-tetanus vaccine at week 8 (A + DT + P wk 8). Blood glucose levels were determined at the times indicated and levels over 300 mg/dl were considered positive.

### Hemophilus Vaccine Figures

**Figure 2A:** All children born in Finland between October 1st, 1985 and August 31st, 1987, approximately 116,000 were randomized to receive 4 doses of the HiB vaccine (PPR-D, Connaught) starting at 3 months of life or one dose starting at 24 months of life. By design of the original study historical controls were designated as the unvaccinated controls for long term safety studies. An control group which did not receive the HiB vaccine, a cohort included all 128,500 children born in Finland in the 24 months prior to the HiB vaccine study. The graph shows the cumulative incidence of IDDM/100,000 in the groups receiving 4, 1, and 0 doses of hemophilus vaccine. The graph is derived form all tabulated data points, including ages 2,5,7, and 10.

**Figure 2Bi:** All children born in Finland between October 1st, 1985 and August 31st, 1987, approximately 116,000, were randomized to receive 4 doses of the HiB vaccine (PPR-D, Connaught) starting at 3 months of life or one dose starting at 24 months of life. The data shows the two randomized groups separate between 3-4 years of life and then become parallel until age 10. The results indicate a clustering of cases of IDDM occurring during a 6 month period between ages 3 and 4.

**Figure 2Bii:** All children born in Finland between October 1st, 1985 and August 31st, 1987, approximately 116,000 were randomized to receive 4 doses of the HiB vaccine (PPR-D,

Connaught) starting at 3 months of life or one dose starting at 24 months of life. The incidence of IDDM was also calculated in an control group which did not receive the HiB vaccine, a cohort which included all 128,500 children born in Finland in the 24 months prior to the HiB vaccine study. The data shows the curves of the cumulative incidence of IDDM in the group receiving 1 dose and the controls separated around 5.5 years of life, 3.5 years after the administration of the HiB vaccine, and then became parallel until age 10. The results indicate a clustering of cases of IDDM occurring during a 6 month period starting at 5.5 years of life.

**Figure 2C:** The incidence of IDDM in Finnish children age 5-9 was stable from 1982 to 1993 but rose drastically starting in 1994 when a large number of Hemophilus vaccinated children were in this age group. The unvaccinated control group from the hemophilus clinical trial had an incidence of IDDM similar to the unvaccinated children between the years 1982-1993 while the vaccinated group of children had an incidence of IDDM similar to the Finnish children age 5-9 in the years 1994-1996. This indicates that there was a rapid rise in the incidence of IDDM that was specific for the vaccinated children.

**Figure 2D:** The incidence of IDDM in children age 1-4 in Finland.

**Figure 2E:** The incidence of IDDM in Finnish children age 1-4 was stable from 1986 to 1993 but rose drastically starting in 1994 when a large number of Hemophilus vaccinated children were immunized. The unvaccinated control group from the hemophilus clinical trial had an incidence of IDDM similar to the baseline incidence of IDDM while the vaccinated group of children had an incidence of IDDM similar to the Finnish children age 1-4 in the years 1994-1996. This indicates that there was a rapid rise in the incidence of IDDM that was specific for the vaccinated children.

**Figure 2F:** The hemophilus influenza B vaccine was offered to infants in the Oxford regions of the UK starting May 1, 1991 in three of the region's eight districts and July 1, 1991, in a fourth district. Over 90% of infants had been immunized by October 1, 1992. Starting in October of 1992 the vaccine was offered to all children under 5 in the UK. The incidence of IDDM rose 33% acutely in the Oxford region in children under age 5 starting in 1994. This follows the same approximate 2-4 year delay between immunization with the hemophilus vaccine in Finland and the rise in IDDM.

**Figure 2G:** Starting in October of 1992 the hemophilus vaccine was offered to all children under 5 in the UK. The incidence of IDDM rose Yorkshire region in children under age 5 starting in 1995. This follows the same approximate 2-4 year delay between immunization with the hemophilus vaccine in Finland and the rise in IDDM.

**Figure 2H:** The incidence of IDDM in Devon and Cornwall in children age 0-4 rose during the interval 1990-1996 after the addition of the hemophilus (1992) and mumps rubella vaccine (1988).

**Figure 2I:** Starting in October of 1992 the hemophilus vaccine was offered to all children under 5 in the UK. The incidence of IDDM rose Yorkshire region in children 5-9 starting in 1996, one year after it rose in children age 0-4. This follows the same approximate 2-4 year delay between immunization with the hemophilus vaccine in Finland and the rise in IDDM.

**Figure 2J:** The hemophilus influenza B vaccine was offered to infants in the Oxford regions of the UK starting May 1, 1991 in three of the region's eight districts and July 1, 1991, in a fourth district. Over 90% of infants had been immunized by October 1, 1992. Starting in October of 1992 the vaccine was offered to all children under 5 in the UK. The incidence of IDDM rose acutely in the Oxford region in children age 5-9 starting in 1995, one year after it rose in children age 0-4. This follows the same approximate 2-4 year delay between immunization with the hemophilus vaccine in Finland and the rise in IDDM.

**Figure 2K:** Rises in the incidence of IDDM occurred in Iceland after the addition of the vaccine to the immunization schedule in 1989.

**Figure 2L:** Rises in the incidence of IDDM occurred in New Zealand after the addition of the vaccine to the immunization schedule in 1994. Data is not currently available for years 1995 through 1997.

**Figure 2M:** Rises in the incidence of IDDM have also been reported in the US after the introduction of the HiB vaccine. An epidemic of diabetes in the 0-4 age group occurred during the years 1985-1989 in Allegheny county at a time when the Hemophilus influenza vaccine was being incorporated into the immunization schedule. The FDA approved the Hemophilus influenza polysaccharide vaccine in 1985 and the conjugated vaccine in 1987. The vaccine was widely administered to children in Allegheny county, a study of its efficacy performed in Allegheny county showed that about 36% of children, chosen as controls, were immunized with the vaccine between August of 1985 and July of 1987.

**Figure 2N:** A seven center collaborative study looked for an association between vaccines and the development of IDDM showed that the hemophilus vaccine was associated with an odds ratio of 1.16 (105). A second study looking at the development of autoantibodies following hemophilus vaccination found the hemophilus vaccine associated with an odds ratio of 1.18 which is similar to the relative risk of 1.17 found with the 4 dose hemophilus vaccinated children followed until age 10 in Finland.

## Hepatitis B Vaccine Figures

**Figure 3A:** The incidence of type I diabetes in the 0-19 year old age group has been studied prospectively since 1982 in Christchurch, New Zealand. New Zealand government instituted a massive Hepatitis B vaccination program in 1988 which was extended to include all children under 16. The incidence of type I diabetes in persons 0-19 years old living in Christchurch was stable prior to the vaccine program but increased in the years after 1988.

The mumps rubella vaccine was also added to the immunization schedule in 1990.

**Figure 3B:** Dr. Robert Elliott presented data at the International Society for Pediatric and Adolescent Diabetes, September 1998, Zurich . The incidence of type 1 diabetes (IDDM) rose in children following the introduction of the hepatitis B vaccine. The mumps rubella vaccine was also added to the immunization schedule in 1990.

**Figure 3C:** Dr. Robert Elliott presented data at the International Society for Pediatric and Adolescent Diabetes, September 1998, Zurich . The data shows birth cohorts immunized with the hepatitis B vaccine have an increased risk of type 1 diabetes.

**Figure 3D:** A US government funded study was conducted to confirm the findings in New Zealand. The preliminary data found and increased risk of type 1 diabetes when the hepatitis B vaccine was given starting after two months. The odds ratio was 1.9 with an average follow up of 22 months which was similar to the finding in New Zealand, relative risk of 1.6 with 3 year follow up.

**Figure 3E:** The hepatitis B vaccine was given to children age 3 month and 12 years starting in 1991. There was no catch-up program and immunization rates were as low as 30%. A birth cohort study looked at children immunized starting at 3 months of life or at age 12. The children vaccinated at 3 months had an increased risk of IDDM compared of control cohorts of 1.24 when followed to age 6. The children immunized at age 12 had an increased risk of IDDM compared of control cohorts of 2.2 when followed to age 15. The weighted average relative risk was 1.4 for these low immunized cohorts ($P<0.05$).

**BCG Vaccine Figures**

**Figure 4A:** An comprehensive study on the incidence of IDDM in countries in Western Europe shows that those countries giving the BCG vaccine starting after 2 months of age, most commonly at school age, have an increased incidence of diabetes. This ecological study indicates BCG immunization starting after two months is associated with a relative risk of 1.74 . The incidence of IDDM in Denmark in 1989 was 18.6 cases/ 100,000 which was similar to other countries giving BCG vaccine at school age, but considerably higher than its former colony Iceland which did not give the BCG vaccine.

**Figure 4B:** Denmark discontinued routine BCG immunization around 1990. The incidence of IDDM in Denmark declined 38% in the years from 1989-1994. The incidence of IDDM in 1989 was 18.6 cases/ 100,000 which was similar to other countries giving BCG vaccine at school age, however after discontinuing the vaccine the incidence approached that of countries not giving the BCG vaccine, including its former colony Iceland.

**Figure 4C:** Denmark discontinued routine BCG immunization around 1990. The incidence of IDDM in Denmark declined 38% in the years from 1989-1994. The incidence of IDDM in 1989

was 18.6 cases/ 100,000 which was similar to other countries giving BCG vaccine at school age, however after discontinuing the vaccine the incidence approached that of countries not giving the BCG vaccine, including its former colony Iceland.

**Figure 4D:** Data from a case control study from Quebec confirmed ecological data that the BCG vaccine when given starting after 2 months of life is associated with an increased risk of IDDM. These are similar to the European ecological data, and the results from Denmark.

**Figure 4E:** An comprehensive study on the incidence of IDDM in countries in Western Europe shows that those countries giving the BCG vaccine starting after 2 months of age, most commonly at school age, have an increased incidence of diabetes compared to those immunized at birth . The incidence of IDDM in Northern Ireland in 1989 was 16.6 cases/ 100,000 which was similar to other countries giving BCG vaccine at school age, but considerably higher than the Republic of Ireland which gives the BCG vaccine at birth.

## Measles Mumps Rubella (MMR) Vaccine Figures

**Figure 5A:** The vaccine regiment in Finland was altered to replace the measles vaccine with the measles, mumps, rubella, vaccine and given at age 14 month and 6 years in 1982. In Finland the incidence of IDDM in children age 1-4 had been stable from 1977-1985 using averages over 3 year periods. A rise was seen in the period 1986-1988, consistent with a 3-4 year delay between immunization and the development of IDDM. The relative risk for immunization with the mumps rubella vaccine was 1.29.

**Figure 5B:** The MMR vaccine replaced the measles vaccine in the UK starting in 1988. A rise in the incidence of IDDM was seen in the 0-4 year olds. The risk ratio associated with the mumps rubella vaccine is 1.23.

**Figure 5C:** A seven center collaborative study looked for an association between vaccines and the development of IDDM showed that the rubella vaccine was associated with an odds ratio of 1.2 . This compares to a relative risk of 1.29 determined by an ecological study in Finland, and 1.23 in Oxford region of the UK.

## Pertussis Vaccine Figures

**Figure 6A:** In 1976 the Finnish government started immunizing children with a more antigenic pertussis vaccine. The incidence of IDDM rose in children age 1-4 rose about 3 years after the introduction of this new vaccine.

**Figure 6B:** In 1976 the Finnish government started immunizing children with a more antigenic pertussis vaccine. Cohort data shows those birth cohorts that received the more potent vaccine had an increased risk of IDDM.

**Figure 6C:** The incidence of type 1 diabetes in the 5-9 age group remained consistently below 34 cases /100,000 but rose to 38 cases/ 100,000 and remained elevated starting around 1982, approximately 5 years after the more potent pertussis vaccine was given to children starting around 3 months of life in 1976.

**Figure 6D:** Sweden discontinued the pertussis vaccine in 1979 and children born in 1980 did not receive the pertussis. Starting in 1982 the MMR (measles mumps rubella) vaccine was offered instead of the measles vaccine to children born in 1980 and later at the age of 18 months. A cohort analysis showed that those cohorts receiving the Pertussis vaccine but not the MMR vaccine had a similar cumulative incidence of IDDM as those receiving the MMR vaccine but not the pertussis vaccine. The effect of the pertussis vaccine on IDDM equals the effect on the mumps rubella vaccine.

**Figure 6E:** During the period of 1975 to 1979 immunization with the pertussis vaccine dropped in the United Kingdom where acceptance rate fell from approximately 75% in 1974 to 30% in 1978 (172). Data from Yorkshire showed a drop in the incidence of IDDM in children age 0-4 which reached a trough in 1982, 3 years after the tough in immunization rates with the pertussis vaccine. Immunization rates are expressed as %/10 in order to fit to scale. The incidence of IDDM went from 9.5 cases of IDDM/100,000 in 1979 to approximately 6.5 in 1982 and back to 9.8 in 1985. The rise in IDDM correlated with the rise in the immunization rate. Between 1979 and 1986 the immunization rate went up 75% and the incidence of IDDM rose 85% from 1982-1989.

## Smallpox Vaccine Figures

**Figure 9A:** Western Europe had major epidemics of smallpox centered around the years 1962 and 1966. The epidemic in 1962 actually started in 1961, continuing into 1963 and included 158 cases from 7 western European countries. The 1966 epidemic included 72 cases and was limited to the United Kingdom. There was a strong emphasis placed on vaccination during the smallpox epidemic of 1961-1963 as demonstrated by World Health Organization statistics showing 23.5 million Europeans were vaccinated with the smallpox vaccine in 1962 compared to an norm of about 11 million in non epidemic years . Children born during years of a smallpox epidemic were likely to have received the smallpox vaccine earlier in life and this explains the inverse correlation between the number of dose of smallpox vaccine administered and the cumulative risk of IDDM in Dutch birth cohorts.

## Military Immunization Figures

**Figure 20A:** Navy men Vs controls

The incidence of IDDM in highly immunized white men serving in the US navy aged 17-35 was compared to the incidence of IDDM for adult men age 15-35 from several Western European countries. All of the Western European countries had laws drafting men. The incidence of IDDM in young US military personnel, age 17 to 19 is initially in par with the European populations. However, the incidence of IDDM in the highly immunized US navy personnel increases gradually with time compared to comparable (but less highly immunized) conscripts from European countries. The relative risk of IDDM in the US navy increased from 1.3 (1.17-1.51) at age 20-24 to 2.5 times (2.01-3.03) at age 30-34. The in the incidence of IDDM in conscripted European men was fairly constant from 13.5 cases/ 100,000 in the 15-19 age group to 13.2 in the 30-34 age group, relative risk .97 (.82-1.16). By contrast the incidence of IDDM in the highly immunized US navy men increases from 12.5 cases/ 100,000 in the 17-19 age group to 32.4 cases/ 100,00 in the 30-34 age group, relative risk 2.59 (2.07-3.24).

**Figure 20B:** Navy women Vs controls

The incidence of IDDM in highly immunized white women serving in the US navy aged 17-35 was compared to the incidence in adult women age 15-35 from several Western European countries. None of the Western European countries had laws drafting women. A rise in the relative risk of IDDM is seen in US navy women compared to controls. The relative risk rises from 3.0 (2.26-4.07) at age 20-24 to 5.6 (2.9-10.85) at age 30-34. The incidence of IDDM declines with time in the non conscripted European women from 10.6 cases/ 100,000 in the 15-19 age group to 5.9 cases/ 100,000 in the 30-34 age group, relative risk .56 (0.44-0.72) . By contrast in the heavily immunized navy women the incidence of IDDM increases from 12.6 cases/ 100,000 in the 17-19 age group to 33.2 cases/ 100,000 in the 30-34 age group, relative risk 2.63 (1.04-6.69) .

**Figure 20C:** US navy women Vs men

The incidence of IDDM in white men serving in the US navy aged 17-35 was compared to the incidence of IDDM in white women serving in the US navy aged 17-35. in the US military personnel the risk of IDDM is slightly lower in men then women, relative risk 0.8 (0.64-0.97).

**Figure 20D:** Conscripted men Vs women

The incidence of IDDM for conscripted adult men age 15-35 from several Western European countries was compared to the incidence of IDDM in women living in the same Western European countries. All of the Western European countries had laws drafting men but not women. The incidence of IDDM starts about the same in men and women however the

incidence in the conscripted men increases relative to the non conscripted women. In those 20 or older the relative risk of IDDM in men versus women is 1.68 (1.53, 1.84) .

**Fig. 1A: Effect of DTP vaccine on diabetes female NOD mice**

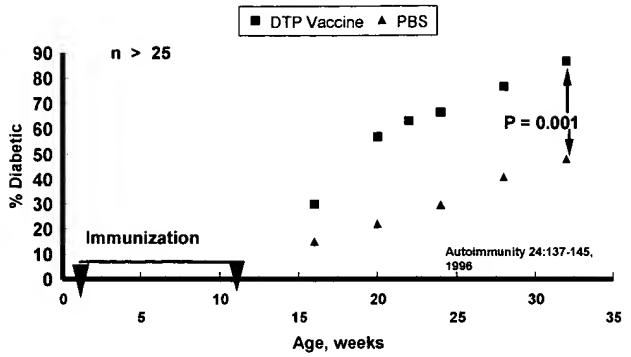



**Fig. 1B: Effect of pertussis vaccine of diabetes female NOD mice**

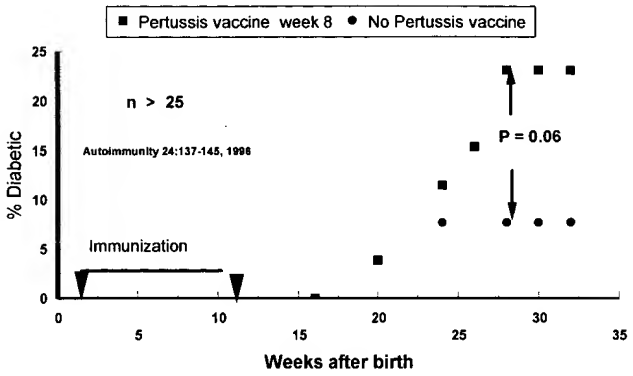



**Fig. 2A: Effect of Hemophilus vaccine on type 1 diabetes Finnish vaccine trial**

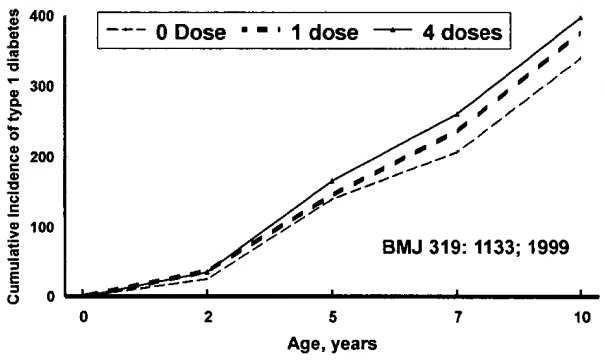



**Fig. 2Bi: Effect of Hemophilus vaccine on type 1 diabetes Finnish vaccine trial**

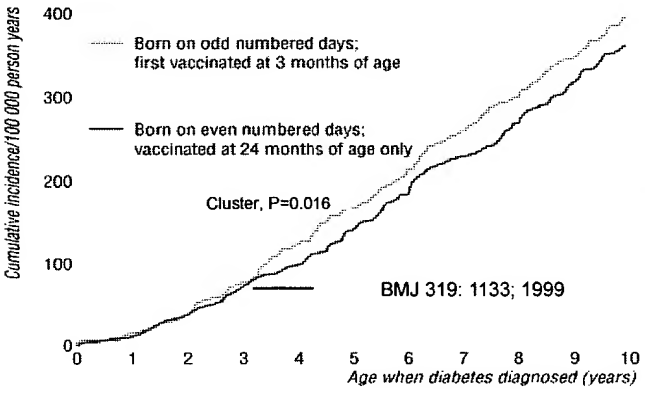



**Fig. 2Bii: Effect of Hemophilus vaccine on type 1 diabetes Finnish vaccine trial**

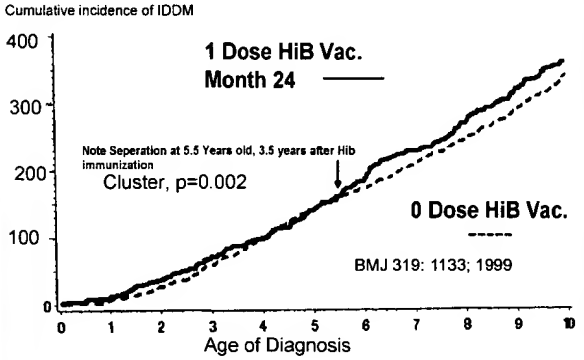



**Fig. 2C: Effect of Hemophilus vaccine on type 1 diabetes Finnish vaccine trial: 5-9 year olds**

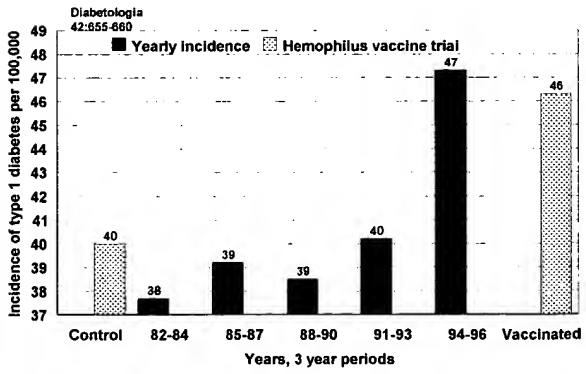


Fig. 2D: Incidence of type 1 diabetes in Finland children: 1-4 year old

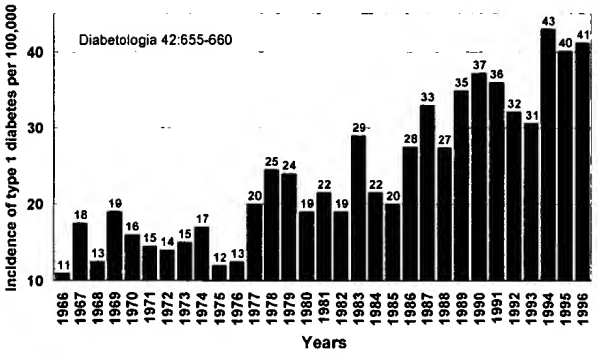



Fig. 2E: Effect of the Hemophilus vaccine on type 1 diabetes
Finnish vaccine trial: 1-4 year olds

Diabetologia 42:655-660; 1999 BMJ 319: 1133 ; 1999

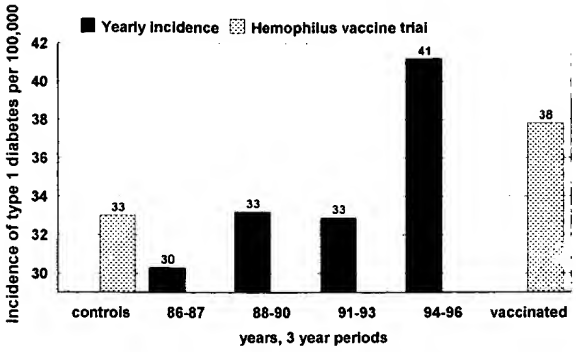



Fig. 2F: Effect of the hemophilus vaccine (started 1991) on type 1 diabetes
Oxford, England: 0-4 year olds

BMJ 315: 713-716, 1997

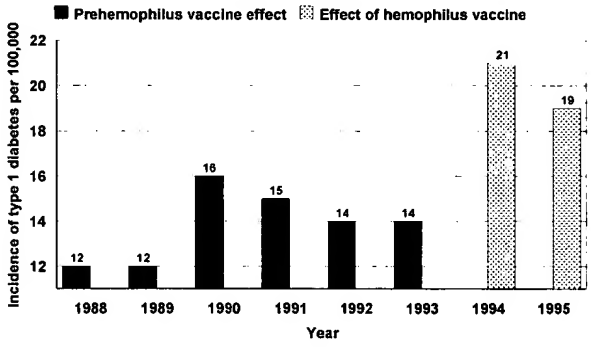



Fig. 2G: Effect of the hemophilus vaccine (started 1992) on type 1 diabetes
Yorkshire , England: 0-4 year olds
Data: 3 year running averages

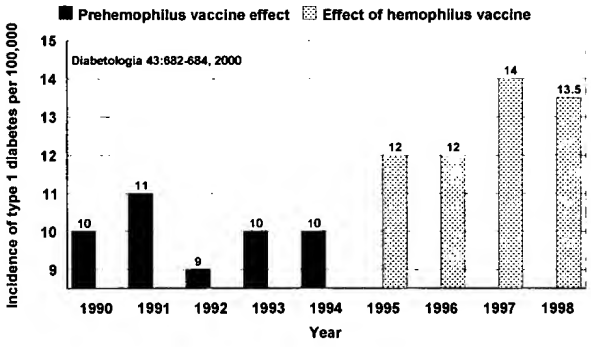



Fig. 2 H: Effect of the hemophilus vaccine and mumps rubella on IDDM
Devon & Cornwall, UK: 0-4 year olds

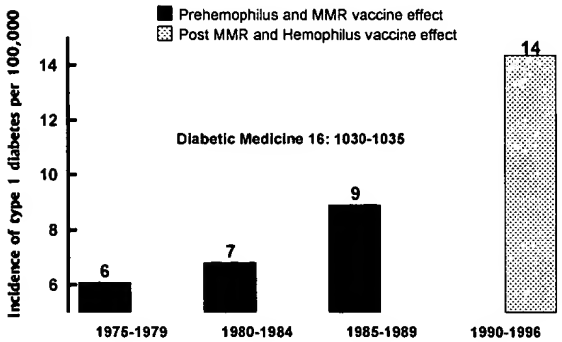



Fig. 2I: Effect of the hemophilus vaccine (started 1992) on type 1 diabetes
Yorkshire , England:5-9 year olds

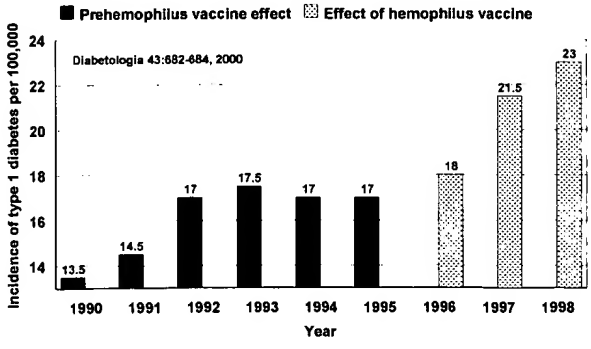


Fig 2J.: Effect of the hemophilus vaccine (started 1991) on type 1 diabetes
Oxford, England: 5-9 year olds

BMJ 315: 713-716, 1997

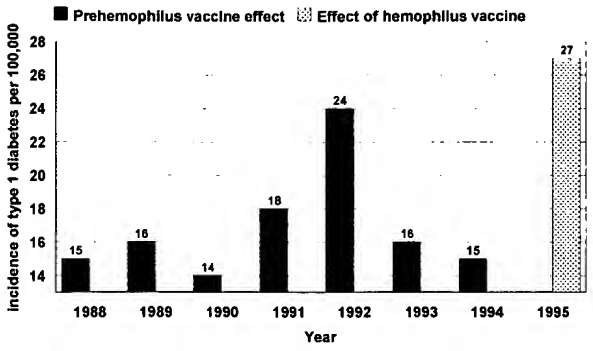



Fig 2K: Effect of the Hemophilus Vaccine (started 1988) on type 1 diabetes
Iceland
relative risk of 1.25

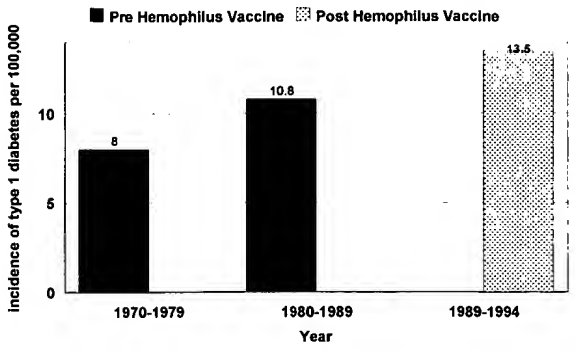



Fig. 2L: Effect of the hemophilus B vaccine (started 1994) on type 1 diabetes
Southern New Zealand: 0-19 year olds

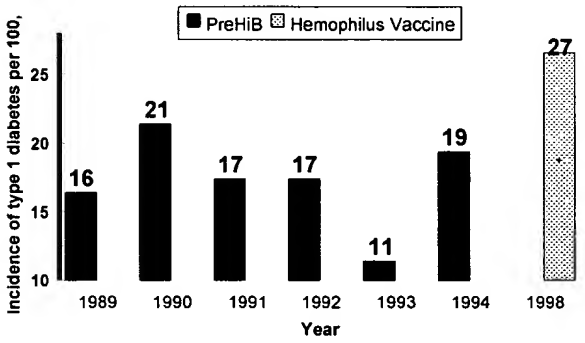



Fig 2M: Effect of the hemophilus vaccine on type 1 diabetes
Pittsburgh: 0-4 year olds, whites

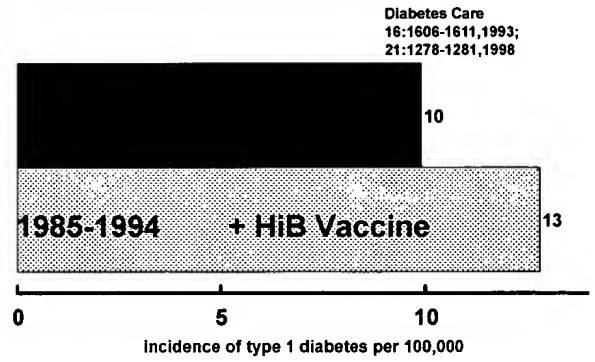



Fig. 2N: Effect of the Hemophilus vaccine on type 1 diabetes
similar risk in many separate studies

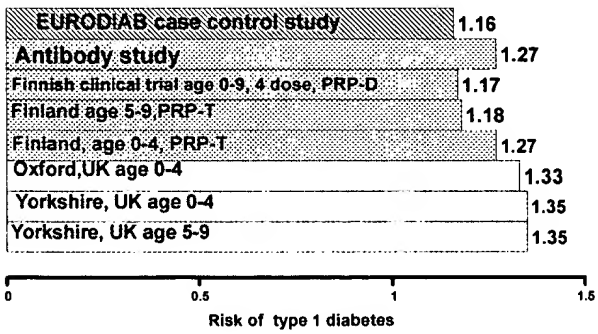



Fig. 3A: Effect of the hepatitis B vaccine on type 1 diabetes
Southern New Zealand: 0-19 year olds

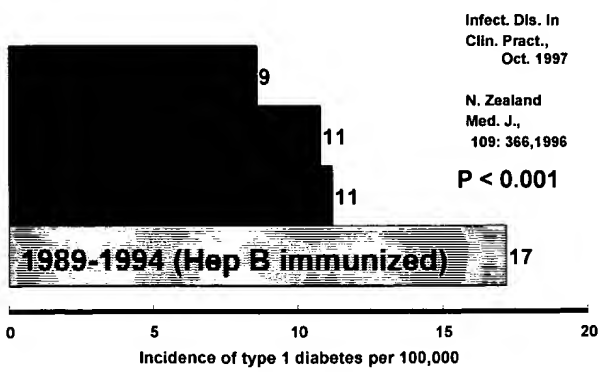


Fig. 3B: Effect of the Hepatitis B vaccine on diabetes
Auckland (North Island) New Zealand: children

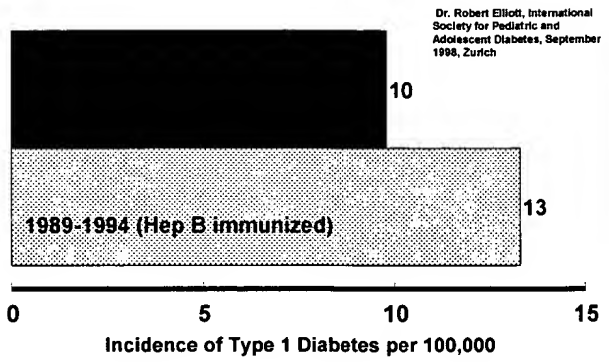



Fig. 3C: Effect of Hepatitis B vaccine on type 1 diabetes
Northern (Auckland) New Zealand: birth cohorts under age 5

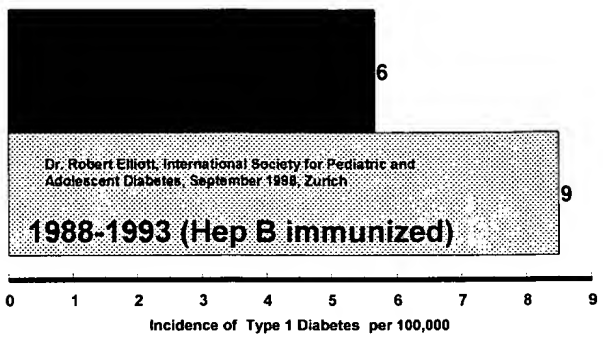



Fig. 3D: Effect of the Hepatitis B vaccine on type 1 diabetes
similar risk in two separate studies

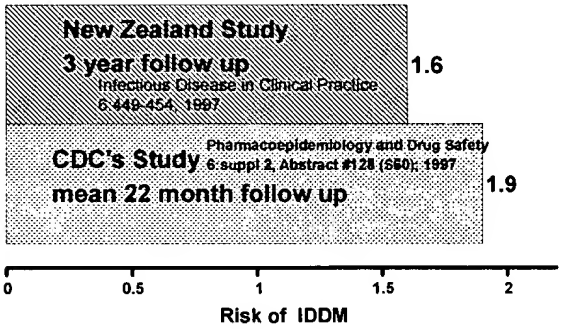



Fig. 3E: Effect of the Hepatitis B Vaccine on type 1 diabetes
Italy

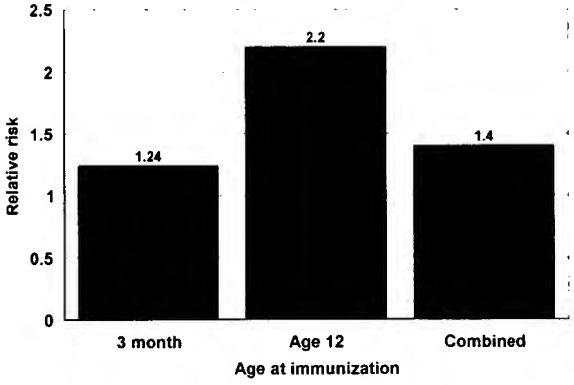



Fig. 4A: Effect of school BCG vaccine on type 1 diabetes
Western Europe: 0-14 year olds

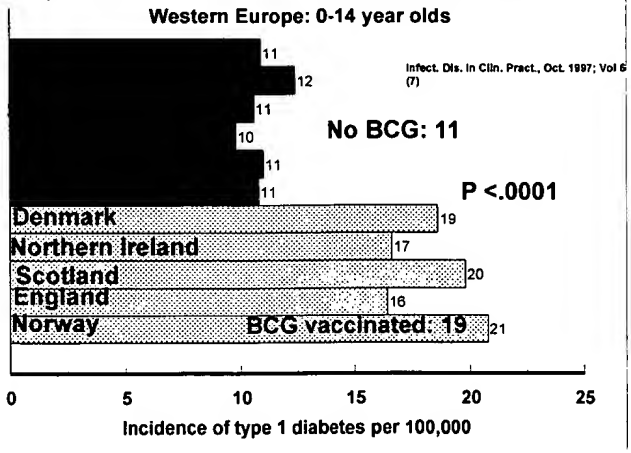



Fig. 4B: Effect of school BCG vaccine on type 1 diabetes
Western Europe: 0-14 year olds

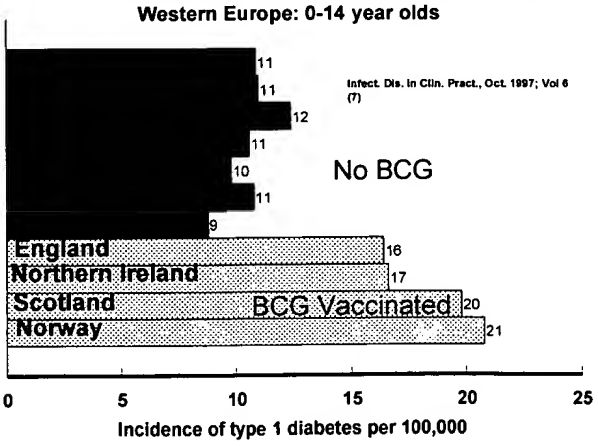


Fig. 4C: Comparison of incidence of type 1 diabetes in Iceland and Denmark before and after discontinuation of BCG in Denmark

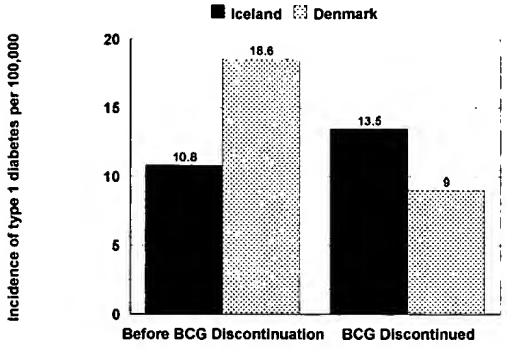



Fig 4D: Effect of late BCG vaccination on type 1 diabetes similar relative risk in three separate studies

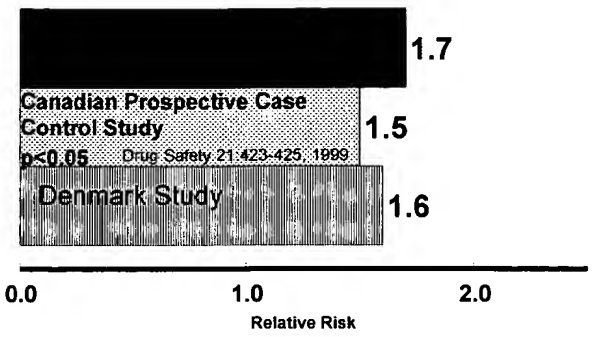



Fig. 4E: Effect of BCG vaccine on type 1 diabetes
Western Europe: 0-14 year olds

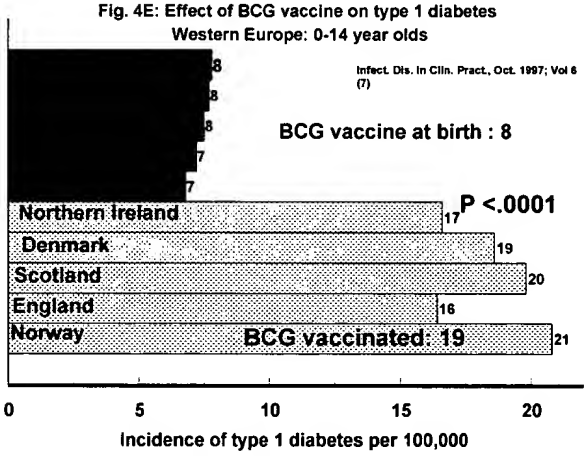



Fig. 5A: Effect of Measles, Mumps, Rubella, vaccine on type 1 diabetes
Finland: 1-4 year olds

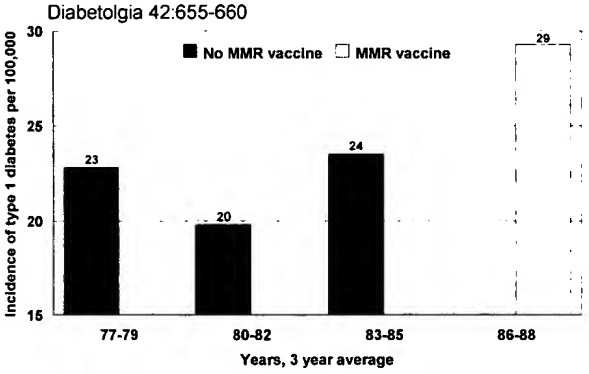



Fig. 5B: Effect of the MMR vaccine (started 1988) on type 1 diabetes
UK, 3 regions : 0-4 year olds
relative risk of 1.23

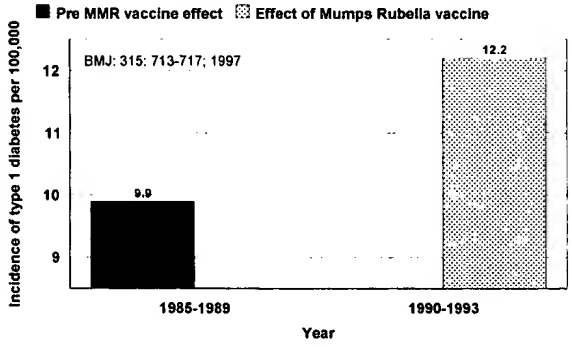



Fig. 5C: Effect of the Rubella (/Mumps) vaccine on type 1 diabetes
similar risk in many different studies

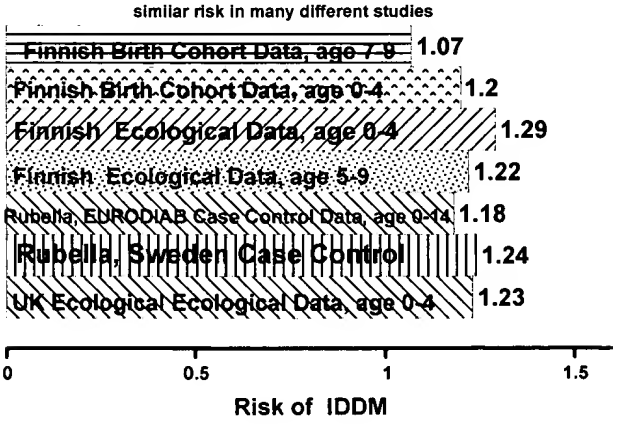


Fig. 6A: Effect of Pertussis vaccine on type 1 diabetes
Finland: 1-4 year olds

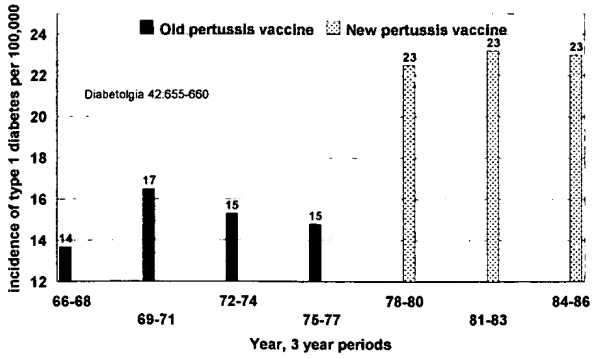



Fig. 6B: Effect of Pertussis vaccine on type 1 diabetes
Finland: 0-4 year olds
Relative risk: 1.25

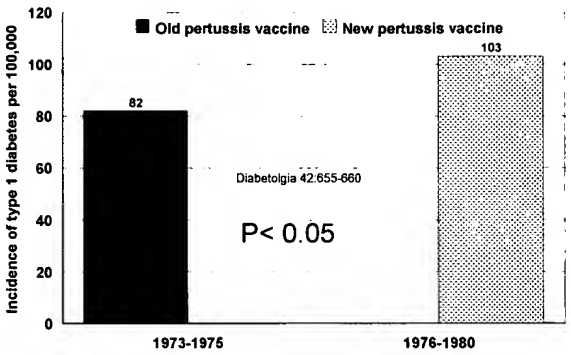



Fig 6C: Effect of Pertussis and MMR vaccines on type 1 diabetes
Finland: 5-9 year olds

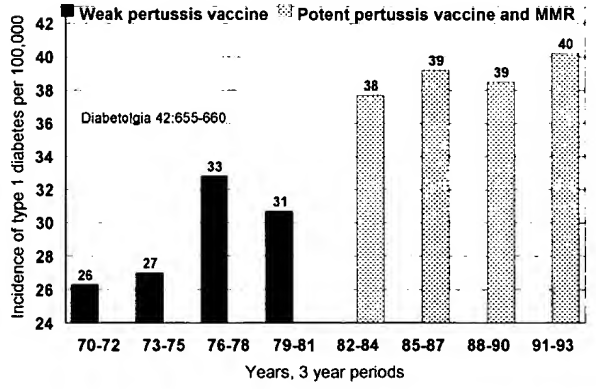



Fig 6D: Effect of Pertussis or MMR vaccines on type 1 diabetes
Sweden birth cohorts through age 12

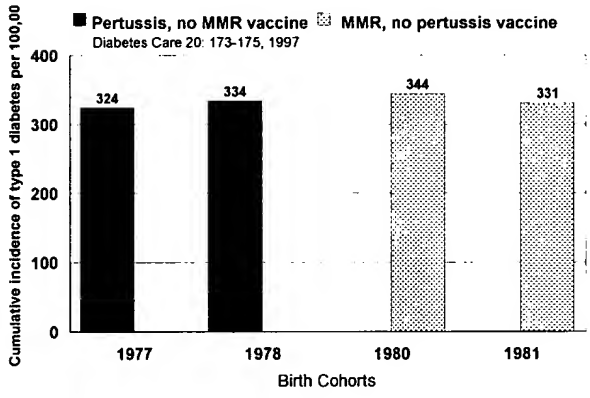



Fig. 6E: Incidence of type 1 diabetes
correlates with pertussis immunization rates in UK

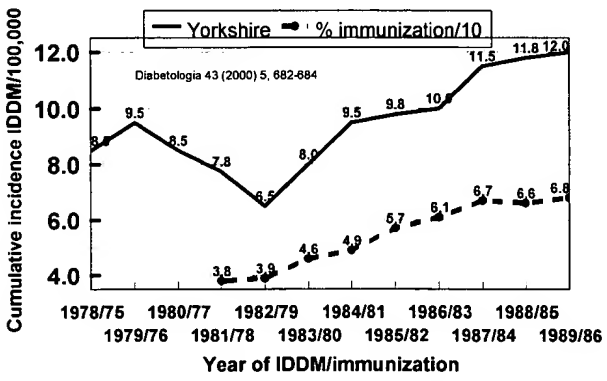



Fig. 9A: Smallpox vaccine usage and
cumulative risk of type 1 diabetes

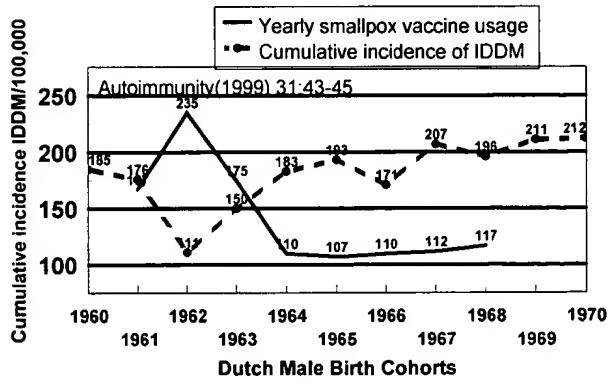


Fig. 20A: Type 1 diabetes in highly immunized white US Navy men vs controls

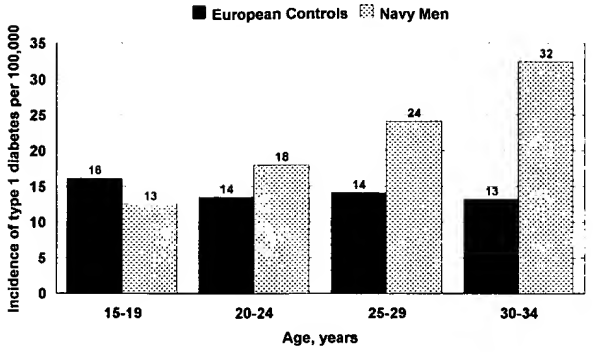



Fig 20B: Type 1 diabetes in highly immunized white US Navy women vs controls

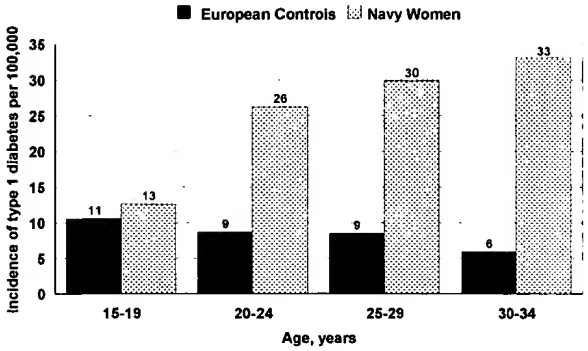



Fig. 20C: Type 1 diabetes in highly immunized US Navy women vs men (US boys vs girls)

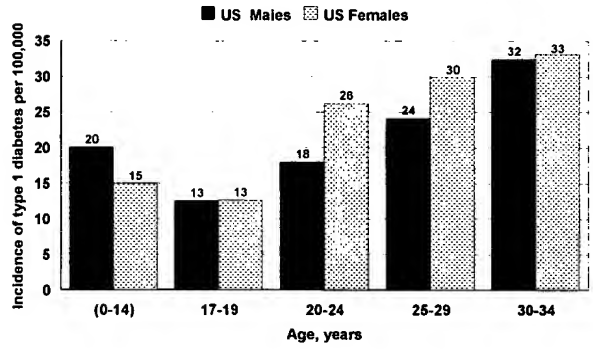
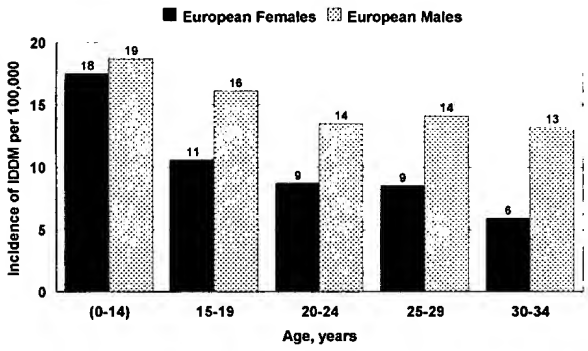



Fig. 2D: Type 1 diabetes higher in European conscripted men than nonconscripted European women (boys vs girls)



## Table 0A. Criteria for Using Epidemiology to Establish Proof of a Causal Relationship

| Vaccines | Hemophilus | Hepatitis B | BCG | Mumps/ Rubella | Pertussis | Small Pox |
|---|---|---|---|---|---|---|
| Data from prospective controlled clinical trials | Fig:2A,2Bi,2Bii | | | | | |
| Rises in incidence of IDDM post immunization in groups where incidence previously constant | Fig:2C | Fig:3A | | Fig:5A | Fig:6A | |
| "Step up" in the incidence of IDDM in groups where incidence had been rising gradually | Fig:2E,2F,2G,2H | Fig:3B,3C | | Fig:5B | Fig:6C | |
| Temporal associations between immunization and the development of IDDM | Fig:2Bi,2Bii | | | | | |
| Changes in the age of diagnosis (onset) of IDDM following immunization | | | | | | |
| Congruency between several different studies and even different types of studies | Fig:2N | Fig:3D,3E | Fig:4D | Fig:5C | Fig:6B | |
| Declines in the incidence of IDDM following discontinuation of vaccine | | | Fig:4C | | Fig:6E | |
| Differences in incidence depending on the timing of administration | | | Fig:4E | | | Fig:9A |

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# Table 1A, Effect of Immunization on Diabetes in Female NOD Mice

| | Group Size | % Diabetic | P values | | |
|---|---|---|---|---|---|
| **Experiment 1** | | WK 36 | | | |
| **PBS** | n=20 | 75.0% | **XXXXX** | | |
| Anthrax Vaccine | n=19 | 42.1% | **.0438, (0.0219)** | | |
| **Experiment 2** | | WK 32 | | | |
| **DTP wk 8** | n=30 | 86.7% | **XXXXX** | | |
| **PBS** | n=27 | 48.1% | **.0028** | **XXXXX** | |
| Anthrax Vaccine | n=29 | 13.8% | **<0.0001** | **0.007** | |
| **Anthrax Vaccine + DT** | n=26 | 7.7% | **<0.0001** | **0.002** | **XXXXX** |
| Anthrax Vaccine + DT + P wk 8 | n=26 | 23.1% | **<0.0001** | **0.063** | **.130, (0.065)** |
| Anthrax Vaccine + DTP | n=29 | 0.0% | **<0.0001** | **<0.0001** | |

P value calculated using 2 tail and 1 tail (x) test

All P values calculated comparing the per cent diabetic to that in the group above marked by XXXXX

**Source: Autoimmunity 24: 137-145, 1996 (Table 1)**

# Table 2A, Incidence of IDDM in Children Receiving 4, 1, or 0 Doses of Hemophilus Vaccine

| Population | 4 DOSES 59,024 | | 1 DOSE 56,921 | | 4 or 1 DOSE 115,945 | | 0 Dose 128,532 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases IDDM | Cumulative Incidence 100,000 | Cases IDDM | Cumulative Incidence 100,000 | Cases IDDM | Cumulative Incidence 100,000 | Cases IDDM | Cumulative Incidence 100,000 | Incidence Difference 4 doses vs 0 dose | P* (4 vs 0) value | Incidence Difference 4/1doses vs '0 dose | P* (4 or 1 vs 0) value | Incidence Difference 1 doses vs 0 dose | P* (4 vs 0) value |
| Age | | | | | | | | | | | | | | |
| 0 to 10 | 235 | **398** | 214 | **376** | 449 | **387** | 437 | **340** | 58 | 0.029 | 47 | 0.028 | | |
| 0 to 7 | 154 | **261** | 135 | **237** | 289 | **249** | 266 | **207** | 54 | 0.013 | 42 | 0.016 | | |
| 0 to 5 | 98 | **166** | 83 | **146** | 181 | **156** | 180 | **140** | 26 | | 16 | | | |
| 0 to 2 | 21 | **36** | 21 | **37** | 42 | **36** | 33 | **26** | 10 | | 11 | | | |
| 5 to 10 | 137 | **232** | 131 | **230** | 268 | **231** | 257 | **200** | 32 | | 31 | 0.053 | | |
| 2 to 7 | 133 | **225** | 114 | **200** | 247 | **213** | 233 | **181** | 44 | 0.026 | 32 | 0.042 | | |
| 2 to 5 | 77 | **130** | 62 | **109** | 139 | **120** | 147 | **114** | 16 | | 6 | | | |
| 5 to 7 | 56 | **95** | 52 | **91** | 108 | **93** | 86 | **67** | 28 | 0.027 | 26 | 0.013 | 24 | 0.048 |
| 7 to 10 | 81 | **137** | 79 | **139** | 160 | **138** | 171 | **133** | 4 | | 5 | | | |

*Statistics, : one-tailed Fisher calculated using WHO/CDC's EPI-6 program

Source : Source: BMJ 319: 1133

# Table 2B, HiB Vaccine and Clustering of IDDM

| HiB Vaccine | Cases of IDDM Cluster 3.25 Months | Cases of IDDM Cluster 5.75 Months | Population Size | P value 3.25 months | 5.75 months | |
|---|---|---|---|---|---|---|
| 1 Dose | 6.0 | 10.0 | 56,921 | 0.022 | 0.016 | 1 Tailed fisher |
| 4 Doses | 17.0 | 24.0 | 59,024 | 0.027 | 0.022 | Pearson chi square |

# Table 2C, Incidence of IDDM in Allegheny County, Pennsylvania

White Children, Age 0-4

| Year | Incidence of Diabetes (cases/100,000) | |
|---|---|---|
| 1965-1969 | 6.8 | |
| 1970-1979 | 6.4 | |
| 1975-1979 | 2.6 | |
| 1980-1984 | 9.9 | 6.25 |
| 1985-1989 | 16.1 | |
| 1990-1994 | 9.5 | 12.35 |

Source:
Diabetes Care 16:1606-1611,1993
Diabetes Care 21:1278-1281,1998

# Table 3A, Effect of the Hepatitis B Vaccine on IDDM

**Age 0-19, Christchurch, New Zealand**

| Year | Incidence of Diabetes (cases/100,000) | |
|---|---|---|
| 1970 | 5 | Retrospective |
| 1971 | 6 | Average incidence 1970-1975: 8.6 |
| 1972 | 11.4 | Approximate number of cases: 52 |
| 1973 | 7.3 | |
| 1974 | 9.5 | |
| 1975 | 12.5 | |
| 1976 | 9.8 | Retrospective |
| 1977 | 9.8 | Average incidence 1976-1981:10.8 |
| 1978 | 15 | Approximate number of cases:65 |
| 1979 | 9 | |
| 1980 | 7 | |
| 1981 | 14 | |
| 1982 | 12.5 | Prospective |
| 1983 | 12.5 | Average incidence 1982-1987:11.2 |
| 1984 | 13.4 | Approximate number of cases:73 |
| 1985 | 12.5 | |
| 1986 | 8.6 | |
| 1987 | 7.6 | |
| 1988 | 9.6 | Hep B Immunization program begins |
| 1989 | 16.4 | Prospective |
| 1990 | 21.4 | Average incidence 1989-1994:17.2 |
| 1991 | 17.4 | Approximate number of cases:103 |
| 1992 | 17.4 | |
| 1993 | 11.4 | P=0.0001 (comparing 1982-1987 vs 1989-1994) |
| 1994 | 19.4 | P calculated using a normal approximation of a Poisson Distribution **Relative risk : 1.53** |

Source: Infectious Disease in Clinical Practice 6:449-454, 1997
**Source: Russel Scott,**

# Table 3B, Effect of the Hepatitis B Vaccine on IDDM

Incidence of IDDM in Auckland, NZ

| Year | Incidence of Diabetes (cases/100,000) | |
|---|---|---|
| 1977 | 8 | |
| 1978 | 6.5 | |
| 1979 | 7.5 | |
| 1980 | 7 | |
| 1981 | 8.5 | |
| 1982 | 10 | |
| 1983 | 12.75 | |
| 1984 | 9.25 | |
| 1985 | 11.25 | |
| 1986 | 14.5 | Average incidence 1977-1987 |
| 1987 | 12.75 | **9.8** |
| 1988 | 12.25 | Hep B Immunization program begins |
| 1989 | 14.5 | Average incidence 1989-1996 |
| 1990 | 11.5 | **13.3** |
| 1991 | 12.75 | |
| 1992 | 14 | |
| 1993 | 11.25 | Relative Risk: 1.36 |
| 1994 | 11.25 | |
| 1995 | 13 | |
| 1996 | 18 | |

Source: Dr. Robert Elliott, International Society for Pediatric and Adolescent Diabetes, September 1998, Zurich

# Table 4A, Effect of BCG Vaccine on Incidence of IDDM in Denmark

| Year | Cases | Population | incidence/ 100,000 | Source |
|---|---|---|---|---|
| 1989 | 44 | 230,524 | 18.6 | Published |
| 1990 | 47 | 228,535 | 19.8 | Published |
| 1991 | 38 | 227,063 | 16.6 | Published |
| 1992 | 34 | 226,580 | 14.9 | Published |
| 1993 | 38 | 228,172 | 16.8 | Published |
| 1994 | 20 | 227,000 | 8.8 | Calculated |

References

Lancet 355:873-876, 2000
Ugeskr Laeger 159:1257-60, 1997

# Table 4B, Effect of BCG Vaccine on Incidence of IDDM in Sweden

| Birth Cohort | Cases of Diabetes | Cohort Size | Cumulative Incidence /100,000 |
|---|---|---|---|
| 1977 | 320 | 95,098 | 336.49 |
| 1976 | 342 | 97,327 | 351.39 |
| 1974 | 329 | 108,671 | 302.75 |
| 1973 | 345 | 107,582 | 320.69 |

| Analysis of Cohorts | Difference /100,000 | P Values Normal Approximation Poisson Distribution 2 Tail | 1 Tail |
|---|---|---|---|
| (1976&1977) vs (1974&1973) | 32.2 | 0.0726 | 0.0363 |
| 1974 vs 1976 | 48.64 | 0.0057 | 0.0028 |

# Table 5A, Effect of MMR Vaccine on IDDM in Children Age 0-4 , UK

| Vaccine | | Year | Incidence Oxford | Population | Incidence Yorkshire | Population | Incidence Devon | Population | weighted Average | Incidence | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1985 | 3.5 | 512,500 | 9.8 | 700,000 | 11 | 148,606 | 7.5 | | |
| PreMMR-Effect | | 1986 | 9 | 512,500 | 10.0 | 700,000 | 4 | 148,606 | 9.0 | | |
| | | 1987 | 7 | 512,500 | 11.5 | 700,000 | 8.5 | 148,606 | 9.5 | | |
| | | 1988 | 12 | 512,500 | 11.8 | 700,000 | 17 | 148,606 | 12.4 | | |
| x | x | **1989** | **12** | **512,500** | **12.0** | **700,000** | **5** | **148,606** | **11.2** | 9.9 | Pre MMR |
| | | 1990 | 16 | 512,500 | 10.0 | 700,000 | 19 | 148,606 | 13.2 | | |
| MMR-Effect | | 1991 | 15 | 512,500 | 11.0 | 700,000 | 2 | 148,606 | 11.5 | | |
| | | 1992 | 14 | 512,500 | 9.0 | 700,000 | 8 | 148,606 | 10.8 | | |
| x | x | **1993** | **14** | **512,500** | **10.0** | **700,000** | **25** | **148,606** | **13.1** | 12.2 | MMR-Effect |
| | | 1994 | 21 | 512,500 | 10.0 | 700,000 | 14 | 148,606 | 14.6 | | |
| HiB-Effect | | 1995 | 19 | 512,500 | 12.0 | 700,000 | 11 | 148,606 | 14.5 | | |
| | | 1996 | | | 12.0 | 700,000 | 17 | 148,606 | 12.9 | | |
| | | 1997 | | | 14.0 | 700,000 | | | 14.0 | | |
| | | 1998 | | | 13.5 | 700,000 | | | 13.5 | 13.9 | HiB-effect |

Sources
BMJ: 315: 713-717, 1997
Diabetologia 43:682-684, 2000
Diabetic Medicine 16:1030-1035, 1999

# Table 9A, Effect of Smallpox Vaccine on IDDM, Sweden

| Smallpox immunization | Birth Cohort | Cases of Diabetes | Cohort Size | Cumulative Incidence /100,000 | Difference /100,000 |
|---|---|---|---|---|---|
| High | 1973 | 345 | 107,582 | 320.69 | |
| | | | | | 17.94 |
| Low | 1974 | 329 | 108,671 | 302.75 | |
| High | 1976 | 342 | 97,327 | 351.39 | |
| | | | | | 14.9 |
| Low | 1977 | 320 | 95,098 | 336.49 | |
| | | | | Sum total effect of smallpox vaccine | 32.84 |

Source: Infectious Disease in Clinical Practice 6:449-454, 1997 (Table 1)
Source: Diabetologia 39: 500-501, 1996

# Table 20A, Effect of Military Immunization on IDDM, Incidence of IDDM in Europeans and White US Sailors

| | Years | Men 15-19 | | Women 15-19 | | Men 20-24 | | Women 20-24 | | Men 25-29 | | Women 25-29 | | Men 30-34 | | Women 30-34 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Incidence | *Cases* | Incidence | *Cases* | Incidence | Cases | Incidence | *Cases* | Incidence | *Cases* | Incidence | *Cases* | Incidence | *Cases* | Incidence | *Cases* |
| Sweden | 1983-1987 | 18 | *180* | 11.3 | *113* | 17.3 | *173* | 8.3 | *83* | 14.6 | *146* | 8.7 | *87* | 13.4 | ***134*** | 5.9 | *59* |
| Belgium | 1989-1995 | 11 | *21* | 9.2 | *17* | 7.9 | *18* | 8.6 | *19* | 13.4 | *35* | 6.4 | *16* | 12.2 | *32* | 6 | *15* |
| Italy, Turin | 1984-1991 | 10.1 | *69* | 6.1 | *40* | 8.0 | *59* | 4.9 | *34* | 7.0 | *47* | 4.0 | *26* | | | | |
| Italy, Sardin | 1989-1990 | 31.8 | *49* | 13.5 | *20* | 18.9 | *30* | 14.9 | *23* | 25.3 | *34* | 7.5 | *10* | | | | |
| Spain,Catal | 1987-1990 | 13.9 | *138* | 8.8 | *83* | 12.5 | *119* | 7.1 | *66* | 11.2 | *100* | 5.7 | *51* | | | | |
| Norway | 1978-1982 | 19.6 | *157* | 15.4 | *117* | 15.7 | *124* | 13.2 | *100* | 21.1 | *165* | 16.4 | *121* | | | | |
| **Total** | | **16.1** | ***614*** | **10.6** | ***390*** | **13.5** | ***523*** | **8.7** | ***325*** | **14.1** | ***527*** | **8.5** | ***311*** | **13.2** | ***166*** | ***5.9*** | ***74*** |
| | | (AGE 17-19) | | (AGE 17-19) | | | | | | | | | | | | | |
| Navy | 1974-1988 | 12.5 | *125* | 12.6 | *8* | 18 | *421* | 26.2 | *51* | 24.1 | *235* | 29.8 | *24* | 32.4 | *197* | 33.2 | *10* |

Incidence= cases/100,000

# Table 30A, Childhood Vaccines and the Risk of IDDM

**EURODIAB multi-center case control study**

| Vaccine | Odds Ratio | Adjusted Odds Ratio |
|---|---|---|
| Polio | 1.03 | 1.2 |
| Measles | 1.02 | 1.1 |
| Mumps | 1 | 1.03 |
| Rubella | 1.18 | 1.27 |
| Tetanus | 1.2 | 1.56 |
| Diphtheria | 1.09 | 1.27 |
| Pertussis | 0.89 | 0.83 |
| Hemophilus | 1.16 | 0.75 |
| **Combined Risk** | **1.67** | **2.13** |

Source: Diabetologia 43: 47-53, 2000 (Table 2)

# Table 30B, Childhood Vaccines and the Risk of IDDM

| | Odds Ratio/ Relative Risk | p value | Source |
|---|---|---|---|
| Polio | 1.03 | 0.92 | 1 |
| Measles | 1.02 | 0.86 | 1 |
| Mumps | 1 | 0.98 | 1 |
| Rubella | 1.18 | 0.21 | 1 |
| Tetanus | 1.2 | 0.55 | 1 |
| Diphtheria | 1.09 | 0.76 | 1 |
| Pertussis | 1.25 | 0.05 | 2 |
| Hemophilu | 1.17 | 0.029 | 3 |
| Hepatitis B | 1.53 | 0.001 | 4 |
| **Total Risk** | **3.63** | | |

Source


1 Diabetologia 43: 47-53, 2000
2 Diabetologia 36:1303-1308, 1993
3 BMJ 319: 1133, 1999
4 Infectious Disease in Clinical Practice 6:449-454, 1997